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(we will no longer accept paper/disc submissions)

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Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication International Committee of Medical Journal Editors

For detailed instructions regarding style and layout refer to "Uniform requirements for manuscripts submitted to biomedical journals". Copies of this document may be obtained on the website http://www.icmje.org. Articles should be submitted under conventional headings of introduction, methods and materials, results, discussion, but other headings will be considered if more suitable. For Uniform Requirements for Sample References go to http://www.nlm.nih.gov/bsd/uniform_requirements.html.

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A cover letter is required and must state that the manuscript: has not been published elsewhere, except in abstract form is not under simultaneous consideration by another journal. Once a decision is made by the Editor on your manuscript, the CJNS office will send you an Author Release form and a Conflict of Interest form if your manuscript has been accepted for revision.

Abstracts

Original Articles and Case Reports should be accompanied by an abstract of 250 words or less on a separate page, in either English or French. The Journal will provide translation to the other language if required. Abstracts should consist of four paragraphs headed: Background (or Objective), Methods, Results and Conclusions.

Acknowledgements

Acknowledgements, including recognition of financial support, should be typed on a separate page at the end of the text. The SI system (système international d'unités) should be used in reporting all laboratory data, even if originally reported in another system. Temperatures are reported in degrees celsius. English language text may use either British or American spelling, but should be consistent throughout.

References

References should be numbered in the order of their citation in the text. Those cited only in tables and legends for illustrations are numbered according to the sequence established by the first identification in the text of a particular table or illustration.

Titles of journals should be abbreviated according to the style used in Index Medicus. References should list the names of up to six authors; if there are more, cite the first SIX, then et al.

Provide the full title, year of publication, volume number and inclusive pagination for journal articles. Do not reference unpublished or "submitted" papers; these can be mentioned in the body of the text and authors must provide five copies of "submitted" manuscripts.

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For Reference Guidelines
www.nlm.nih.gov/bsd/uniform_requirements.html

Examples of correct forms of reference:

Journals

Rose ME, Huerbin MB, Melick J, Marion DW, Palmer AM, Schiding JK, et al. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res. 2002;935(1-2):40-6.

Chapter in a book

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113.

Tables

Type tables double-spaced on pages separate from the text. Provide a table number and title for each. Particular care should be taken in the preparation of tables to ensure that the data are presented clearly and concisely. Each column should have a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Do not submit tables as photographs.

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Review articles on selected topics are also published. They are usually invited, but unsolicited reviews will be considered. Review articles should be accompanied by an abstract of 150 words or less.

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Correspondence to the Editor concerning matters arising in recent articles are welcome. Correspondence should be limited to two double-spaced pages and may include one illustration and a maximum of four references.

Neuroimaging Highlights

Neuroimaging highlights are selected by the editor-in-chief and neuroimaging highlight editors on the basis of two factors. The first is high quality "state of the art" imaging of a novel and uncommon (or common with an uncommon twist) neurological or neurosurgical disorder. The second factor is the clinical novelty of the case.

Neuroimaging highlights require a figure of several panels that clearly outlines all features of the relevant imaging. For example, for MR images this may require different cuts and sequences, etc. Combining more than one imaging modality strengthens the report. The report may also benefit from a single additional panel in a figure if it is directly relevant, e.g. a pathological image or patient image. The text should include a very brief discussion of the case history confined to the relevant history, pertinent abnormal findings, and clinical course with outcome. An additional one to two paragraphs should briefly describe the neuroimaging panels present, and very briefly review relevant aspects of the literature. Overall, the neuroimaging highlights should be 500 words or less, with no more than 10 references.

Images should be of the highest quality, submitted either as glossy prints or electronically as a tiff file at a minimum of 300 dpi and at a size large enough for the printed journal (i.e. not less than 2" wide).

Suitability for publication is judged by the neuroimaging highlight editors, the editor-in-chief and up to one additional external referee.

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PrAGGRENOX®

Dipyridamole/Acetylsalicylic Acid Capsules
200 mg Extended Release Dipyridamole/25 mg Immediate Release Acetylsalicylic Acid (ASA)
Therapeutic Classification: Antiplatelet Agent

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	capsules, 200mg/25 mg	Non-medicinal ingredients (in alphabetical order): acacia, aluminium stearate, colloidal silicon dioxide, corn starch, dimethicone, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, lactose monohydrate, methacrylic acid copolymer, microcrystalline cellulose, povidone, stearic acid, sucrose, talc, tartaric acid, titanium dioxide, and triacetin. The capsule shell contains gelatine, red iron oxide and yellow iron oxide, titanium dioxide and water.

INDICATIONS AND CLINICAL USE

AGGRENOX is indicated for:

- the prevention of stroke in patients who have had a previous stroke or a transient ischemic attack (TIA).

Pediatrics (< 18 years of age): Safety and effectiveness of AGGRENOX in pediatric patients has not been studied. Therefore, AGGRENOX should not be used in pediatric patients.
ASA should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of ASA in certain viral illnesses.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Due to the ASA component, AGGRENOX is also contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drug products and in patients with the syndrome of asthma, rhinitis and nasal polyps.
- Patients with rare hereditary problems of fructose intolerance and/or galactose intolerance (e.g. galactosaemia) should not take this medicine. AGGRENOX contains approximately 23 mg sucrose and 106 mg of lactose per maximum recommended daily dose.

WARNINGS AND PRECAUTIONS

General

ALCOHOL WARNING
Patients who consume three or more alcoholic drinks every day should be counselled about the bleeding risks involved with chronic, heavy alcohol use while taking AGGRENOX, due to the ASA component.
If a patient is to undergo elective surgery, consideration should be given to discontinue AGGRENOX 10 days prior to surgery to allow for the reversal of the effect.
BLEEDING
As any antiplatelet agents, which cause bleeding, the use of AGGRENOX may increase the risk of bleeding such as skin haemorrhage, gastrointestinal bleeding and intracerebral haemorrhage. The addition of other antiplatelet agents (e.g. Clopidogrel, Ticlopidine) to AGGRENOX may further increase the risk of serious bleeding. Even though no study has been conducted, such combination is not recommended.
Due to the ASA component, the concomitant use of AGGRENOX with either selective serotonin reuptake inhibitors (SSRIs) or corticosteroids can increase the gastrointestinal bleeding.
This product contains 106 mg of lactose and 22.5 mg sucrose per maximum recommended daily dose. Patients with rare hereditary problems of fructose intolerance and/ or galactose intolerance e.g. galactosaemia should not take this medicine.

Carcinogenesis and Mutagenesis

CARCINOGENESIS
In carcinogenicity studies in rats and mice with the combination of dipyridamole and ASA at the ratio of 1:6 over a period of 125 and 105 weeks respectively, no significant tumorigenic effect was observed at maximum doses of 450 mg/kg (corresponding to a share of 75 mg/kg of dipyridamole, 9 times the maximum recommended daily human dose for a 50 kg person on a mg/kg basis [or 1.5-2.1 times on a mg/m2 basis]), and 375 mg/kg ASA, 375 times the maximum recommended daily human dose for a 50 kg person on a mg/kg basis (or 58-83 times on a mg/m^2 basis).

Cardiovascular

AGGRENOX should be used with caution in patients with severe coronary artery disease (e.g. unstable angina or recently sustained myocardial infarction), due to the vasodilatory effect of the dipyridamole component. Chest pain may be aggravated in patients with underlying coronary artery disease who are receiving dipyridamole. Patients being treated with AGGRENOX should not receive additional intravenous dipyridamole. If pharmacological stress testing with intravenous dipyridamole for coronary artery disease is considered necessary, then AGGRENOX should be discontinued twenty-four hours prior to testing, otherwise the sensitivity of the intravenous stress test could be limited.
For stroke or TIA patients for whom ASA is indicated to prevent recurrent myocardial infarction (MI) or angina pectoris, the dose of ASA in AGGRENOX has not been proven to provide adequate treatment for these cardiac indications.

Gastrointestinal

PEPTIC ULCER DISEASE
Patients with a history of active peptic ulcer disease should avoid using AGGRENOX, which can cause gastric mucosal irritation, and bleeding, due to the ASA component.
GI side effects include stomach pain, heartburn, nausea, vomiting, diarrhoea, and gross GI bleeding. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Physicians should inform patients about the signs and symptoms of GI side effects and what steps to take if they occur.

Hematologic

AGGRENOX should be used with caution in patients with inherited (haemophilia) or acquired (liver disease or vitamin K deficiency) bleeding disorders, due to the fact that even low doses of ASA can inhibit platelet function leading to an increase in bleeding time.

Hepatic/Biliary/Pancreatic

Due to the ASA component, AGGRENOX should be avoided in patients with severe hepatic insufficiency.

Renal

Due to the ASA component, AGGRENOX should be avoided in patients with severe renal failure (glomerular filtration rate less than 10 mL/min).

Sexual Function/Reproduction

Fertility studies with dipyridamole revealed no evidence of impaired fertility in rats at oral dosages of up to 1250 mg/kg, 156 times the maximum recommended human dose on a mg/kg basis for a 50 kg person (or 35 times on a mg/m2 basis). ASA inhibits ovulation in rats.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies of AGGRENOX in pregnant women. Because animal reproduction studies are not always predictive of human response, AGGRENOX should be given during the first two trimesters of pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. Due to the ASA component, AGGRENOX should not be prescribed during the third trimester of pregnancy.
Nursing Women: Dipyridamole and ASA are excreted in human breast milk in low concentrations. Therefore, caution should be exercised when AGGRENOX is administered to a nursing woman.
Pediatrics (< 18 years of age): Safety and effectiveness of AGGRENOX in pediatric patients has not been studied. Therefore, AGGRENOX should not be used in pediatric patients.
ASA should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of ASA in certain viral illnesses.

Monitoring and Laboratory Tests

ASA has been associated with elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria and prolonged bleeding time. Over the course of the 24-month study (ESPS2), patients treated with AGGRENOX showed a decline (mean change from baseline) in hemoglobin of 0.25 g/dl, hematocrit of 0.75%, and erythrocyte count of 0.13x106/mm^3.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.
A 24-month, multicenter, double-blind, randomized study (ESPS2) was conducted to compare the efficacy and safety of AGGRENOX with placebo, extended release dipyridamole alone and ASA alone. The study was conducted in a total of 6602 male and female patients who had experienced a previous ischemic stroke or transient ischemia of the brain within three months prior to randomization. Discontinuation due to adverse events in ESPS2 was 27.8% for AGGRENOX, 28.2% for extended release dipyridamole, 23.2% for ASA, and 23.7% for placebo.
Table 2 presents the incidence of adverse events that occurred in 1% or more of patients treated with AGGRENOX where the incidence was also greater than those patients treated with placebo.

Table 2: INCIDENCE OF ADVERSE EVENTS IN ESPS2 REPORTED BY > 1% OF PATIENTS DURING AGGRENOX TREATMENT WHERE THE INCIDENCE WAS GREATER THAT THOSE TREATED WITH PLACEBO

	Individual Treatment Group			
	AGGRENOX	**ER-DP Alone**	**ASA Alone**	**placebo**
Total Number of Patients	**N=1650**	**N=1654**	**N =1649**	**N =1649**
Total Number (%) of Patients With at Least One On-Treatment Adverse Event	**1319 (79.9%)**	**1305 (78.9%)**	**1323 (80.2%)**	**1304 (79.1%)**
Body System/Preferred Term				
Any Bleeding** Severity of bleeding:***				
Mild	84 (5.1%)	53 (3.2%)	82 (5.0%)	52 (3.2%)
Moderate	33 (2.0%)	18 (1.1%)	33 (2.0%)	15 (0.9%)
Severe	23 (1.4%)	4 (0.2%)	19 (1.2%)	5 (0.3%)
Fatal	4 (0.2%)	2 (0.1%)	1 (0.1%)	2 (0.1%)
Body as a Whole – General Disorders				
Pain	105 (6.4%)	88 (5.3%)	103 (6.2%)	99 (6.0%)
Fatigue	95 (5.8%)	93 (5.6%)	97 (5.9%)	90 (5.5%)
Back Pain	76 (4.6%)	77 (4.7%)	74 (4.5%)	65 (3.9%)
Accidental Injury	42 (2.5%)	24 (1.5%)	51 (3.1%)	37 (2.2%)
Malaise	27 (1.6%)	23 (1.4%)	26 (1.6%)	22 (1.3%)
Asthenia	29 (1.8%)	19 (1.1%)	17 (1.0%)	18 (1.1%)
Syncope	17 (1.0%)	13 (0.8%)	16 (1.0%)	8 (0.5%)
Cardiovascular Disorders, General				
Cardiac Failure	26 (1.6%)	17 (1.0%)	30 (1.8%)	25 (1.5%)
Central & Peripheral Nervous System Disorders				
Headache	647 (39.2%)	634 (38.3%)	558 (33.8%)	543 (32.9%)
Convulsions	28 (1.7%)	15 (0.9%)	28 (1.7%)	26 (1.6%)
Gastro-Intestinal System Disorders				
Dyspepsia	303 (18.4%)	288 (17.4%)	299 (18.1%)	275 (16.7%)
Abdominal Pain	289 (17.5%)	255 (15.4%)	262 (15.9%)	239 (14.5%)
Nausea	264 (16.0%)	254 (15.4%)	210 (12.7%)	232 (14.1%)
Diarrhoea	210 (12.7%)	257 (15.5%)	112 (6.8%)	161 (9.8%)
Vomiting	138 (8.4%)	129 (7.8%)	101 (6.1)	118 (7.2%)
Hemorrhage Rectum	26 (1.6%)	22 (1.3%)	16 (1.0%)	13 (0.8%)
Melena	31 (1.9%)	10 (0.6%)	20 (1.2%)	13 (0.8%)
Haemorrhoids	16 (1.0%)	13 (0.8%)	10 (0.6%)	10 (0.6%)
GI Hemorrhage	20 (1.2%)	5 (0.3%)	15 (0.9%)	7 (0.4%)
Musculo-Skeletal System Disorders				
Arthralgia	91 (5.5%)	75 (4.5%)	91 (5.5%)	76 (4.6%)
Arthritis	34 (2.1%)	25 (1.5%)	17 (1.0%)	19 (1.2%)
Arthrosis	18 (1.1%)	22 (1.3%)	13 (0.8%)	14 (0.8%)
Myalgia	20 (1.2%)	16 (1.0%)	11 (0.7%)	11 (0.7%)

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Table 2: INCIDENCE OF ADVERSE EVENTS IN ESPS2 REPORTED BY > 1% OF PATIENTS DURING AGGRENOX TREATMENT WHERE THE INCIDENCE WAS GREATER THAT THOSE TREATED WITH PLACEBO *(cont'd)*

	Individual Treatment Group			
	AGGRENOX	ER-DP Alone	ASA Alone	placebo
Total Number of Patients	**N=1650**	**N=1654**	**N =1649**	**N =1649**
Total Number (%) of Patients With at Least One On-Treatment Adverse Event	**1319 (79.9%)**	**1305 (78.9%)**	**1323 (80.2%)**	**1304 (79.1%)**
Neoplasm				
Neoplasm NOS	28 (1.7%)	16 (1.0%)	23 (1.4%)	20 (1.2%)
Platelet, Bleeding & Clotting Disorders				
Hemorrhage NOS	52 (3.2%)	24 (1.5%)	46 (2.8%)	24 (1.5%)
Epistaxis	39 (2.4%)	16 (1.0%)	45 (2.7%)	25 (1.5%)
Purpura	23 (1.4%)	8 (0.5%)	9 (0.5%)	7 (0.4%)
Psychiatric Disorders				
Amnesia	39 (2.4%)	40 (2.4%)	57 (3.5%)	34 (2.1%)
Confusion	18 (1.1%)	9 (0.5%)	22 (1.3%)	15 (0.9%)
Anorexia	19 (1.2%)	17 (1.0%)	10 (0.6%)	15 (0.9%)
Somnolence	20 (1.2%)	13 (0.8%)	18 (1.1%)	9 (0.5%)
Red Blood Cell Disorders				
Anaemia	27 (1.6%)	16 (1.0%)	19 (1.2%)	9 (0.5%)
Respiratory System Disorders				
Coughing	25 (1.5%)	18 (1.1%)	32 (1.9%)	21 (1.3%)
Upper Respiratory Tract Infection	16 (1.0%)	9 (0.5%)	16 (1.0%)	14 (0.8%)

Note: ER-DP = Extended Release Dipyridamole 400 mg/day; ASA = Acetylsalicylic Acid 50 mg/day.
Note: The dosage regimen for all treatment groups is b.i.d.
** Bleeding at any site, reported during follow-up and within 15 days after eventual stroke or treatment cessation.
*** Severity of bleeding: mild = requiring no special treatment; moderate = requiring specific treatment but no blood transfusion; severe = requiring blood transfusion.
Note: NOS = not otherwise specified

Less Common Clinical Trial Adverse Drug Reactions (<1%)
Adverse reactions that occurred in less than 1% of patients treated with AGGRENOX in the ESPS2 study and that were medically judged to be possibly related to either dipyridamole or ASA are listed below.
Body as a Whole: *allergic reaction, fever*
Cardiovascular: hypotension, flushing
Central Nervous System: coma, dizziness, paraesthesia
Gastrointestinal: gastritis, ulceration and perforation
Hearing & Vestibular Disorders: tinnitus, and deafness. Patients with high frequency hearing loss may have difficulty perceiving tinnitus. In these patients, tinnitus cannot be used as a clinical indicator of salicylism
Heart Rate and Rhythm Disorders: tachycardia, palpitation, arrhythmia, supraventricular tachycardia
Liver and Biliary System Disorders: cholelithiasis, jaundice, abnormal hepatic function
Metabolic & Nutritional Disorders: hyperglycemia, thirst
Platelet, Bleeding and Clotting Disorders: haematoma, gingival bleeding, cerebral hemorrhage, intracranial hemorrhage, subarachnoid hemorrhage
Note: There was one case of pancytopenia recorded in a patient within the AGGRENOX treatment group, from which the patient recovered without discontinuation of AGGRENOX.
Psychiatric Disorders: agitation
Reproductive: uterine hemorrhage
Respiratory: hypernea, asthma, bronchospasm, haemoptysis, pulmonary edema
Special Senses: taste loss
Skin and Appendages Disorders: pruritus, urticaria
Urogenital: renal insufficiency and failure, hematuria

Abnormal Hematologic and Clinical Chemistry Findings
Over the course of the 24-month study (ESPS2), patients treated with AGGRENOX showed a decline (mean change from baseline) in hemoglobin of 0.25 g/dl, hematocrit of 0.75%, and erythrocyte count of 0.13x106/mm^3.

Post-Market Adverse Drug Reactions
The following is a list of additional adverse reactions that have been reported either in the literature or are from post-marketing spontaneous reports for either dipyridamole or ASA.
Body as a Whole: hypothermia, migraine-like headache (especially at the beginning of treatment)
Cardiovascular: angina pectoris, worsening of symptoms of coronary heart disease
Central Nervous System: cerebral edema
Fluid and Electrolyte: hyperkalemia, metabolic acidosis, respiratory alkalosis
Gastrointestinal: pancreatitis, Reyes Syndrome
Hearing and Vestibular Disorders: hearing loss
Hypersensitivity: acute anaphylaxis, laryngeal edema
Liver and Biliary System Disorders: hepatitis, incorporated into gallstones
Musculoskeletal: rhabdomyolysis
Metabolic & Nutritional Disorders: hypoglycemia, dehydration
Blood, Platelet, Bleeding and Clotting Disorders: prolongation of the prothrombin time, prolongation of bleeding time, increased bleeding during and after surgery, disseminated intravascular coagulation, coagulopathy, thrombocytopenia
Reproductive: prolonged pregnancy and labour, stillbirths, lower birth weight infants, antepartum and postpartum bleeding
Respiratory: tachypnea
Skin and Appendages Disorders: rash, alopecia, angioedema, skin haemorrhages such as contusion, ecchymosis and haematoma
Urogenital: interstitial nephritis, papillary necrosis, proteinuria

DRUG INTERACTIONS

Drug-Drug Interactions

Overview
When AGGRENOX is used in combination with acetylsalicylic acid or with warfarin the statements regarding precautions, warnings and tolerance for these preparations must be observed. Because of the increased risk of bleeding, the concomitant administration of heparin, or warfarin with AGGRENOX should be undertaken with caution. The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3- Established or Potential Drug-Drug Interactions

	Effect	Clinical comment
The following drug interactions are associated with the Dipyridamole component of AGGRENOX:		
ADENOSINE	Dipyridamole has been reported to increase the plasma levels and cardiovascular effects of adenosine.	Adjustment of adenosine dosage may be necessary.
CHOLINESTERASE INHIBITORS	The dipyridamole component of AGGRENOX may counteract the anticholinesterase effect of cholinesterase inhibitors, thereby potentially aggravating myasthenia gravis.	Patients should be advised to consult a physician if any worsening of the disease occurs.
The following drug interactions are associated with the ASA component of AGGRENOX:		
ACETAZOLAMIDE	Due to the ASA component, concurrent use of AGGRENOX and acetazolamide can lead to high serum concentrations of acetazolamide (and toxicity) due to competition at the renal tubule for secretion.	Adjustment of acetazolamide dosage may be necessary.
ALCOHOL USE (CHRONIC)	Gastro-intestinal bleeding may increase when acetylsalicylic acid is administered concomitantly during chronic alcohol use.	Patients should be advised to consult a physician if any signs or symptoms of bleeding occur.
ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS	Due to the indirect effect of the ASA component on the renin-angiotensin conversion pathway, the hyponatremic and hypotensive effects of ACE inhibitors may be diminished by concomitant administration of AGGRENOX.	Patients should be advised to consult a physician if any signs or symptoms of decreased renal function such as oedema, or increase in blood pressure occur.
ANTICOAGULANT THERAPY (HEPARIN AND WARFARIN	Patients on anticoagulation therapy are at increased risk for bleeding because of drug-drug interactions and effects on platelets. ASA can displace warfarin from protein binding sites, leading to prolongation of both the prothrombin time and the bleeding time. The ASA component of AGGRENOX can increase the anticoagulant activity of heparin, increasing bleeding risk. Acetylsalicylic acid has been shown to *enhance the effect of anticoagulants* (e.g. coumarin derivatives and heparin) which may result in an increased risk of bleeding.	Patients should be advised to consult a physician if any signs or symptoms of bleeding occur.
ANTIPLATELET DRUGS (CLOPIDOGREL, TICLOPIDINE)	Acetylsalicylic acid has been shown to enhance the effect of antiplatelet drugs (e.g. clopidogrel, ticlopidine) which may result in an increased risk of bleeding.	Patients should be advised to consult a physician if any signs or symptoms of bleeding occur.
ANTICONVULSANTS	The ASA component of AGGRENOX can displace protein-bound phenytoin and valproic acid, leading to a decrease in the total concentration of phenytoin and an increase in serum valproic acid levels. Acetylsalicylic acid has been shown to enhance the effect of valproic acid which may result in an increased risk of rare, but often fatal hepatotoxicity.	Adjustment of phenytoin or valproic acid dosage may be necessary.
BETA BLOCKERS	The hypotensive effects of beta blockers may be diminished by the concomitant administration of AGGRENOX due to inhibition of renal prostaglandins by ASA, leading to decreased renal blood flow, and salt and fluid retention.	Patient should be advised to consult a physician if any signs or symptoms of decreased renal function such as oedema, or increase in blood pressure occur.
CORTICOSTEROIDS	Gastro-intestinal bleeding increase when acetylsalicylic acid is administered concomitantly with corticosteroids.	Patient should be advised to consult a physician if any signs or symptoms of bleeding occur.
DIURETICS	The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of AGGRENOX due to inhibition of renal prostaglandins by ASA, leading to decreased renal blood flow and salt and fluid retention	Patient should be advised to consult a physician if any signs or symptoms of decreased renal function such as oedema occur.
IBUPROFEN	The concomitant administration of ibuprofen in healthy volunteers shortened the platelet aggregation inhibitory effect of ASA.	
METHOTREXATE	The ASA component of AGGRENOX can inhibit renal clearance of methotrexate, leading to bone marrow toxicity, especially in the elderly or renally impaired.	Adjustment of methotrexate dosage may be necessary.
NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)	Due to the ASA component, the concurrent use of AGGRENOX with other NSAIDs may increase bleeding or lead to decreased renal function. Gastro-intestinal bleeding increases when acetylsalicylic acid is administered concomitantly with NSAIDs.	Patient should be advised to consult a physician if any signs or symptoms of bleeding occur.

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Table 3- Established or Potential Drug-Drug Interactions *(cont'd)*

	Effect	Clinical comment
ORAL HYPOGLYCAEMICS	AGGRENOX may increase the effectiveness of oral hypoglycemic drugs, leading to hypoglycaemia.	Patient should be advised to consult a physician if any signs or symptoms of hypoglycaemia occur.
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)	Selective serotonin reuptake inhibitors (SSRIs) may increase the risk of bleeding.	Patient should be advised to consult a physician if any signs or symptoms of bleeding occur.
URICOSURIC AGENTS (PROBENECID AND SULFINPYRAZONE) AND NATRIURETIC AGENTS	The ASA component of AGGRENOX antagonizes the uricosuric action of uricosuric agents. ASA decreased the natriuretic effect of spironolactone in healthy volunteers.	Patient should be advised to consult a physician if any signs or symptoms of decreased renal function such as oedema occur.

Drug-Herb interaction

Pharmacokinetic studies to determine the effect of herb or food have not been conducted with AGGRENOX.

Drug-laboratory interactions

Pharmacokinetic studies to determine the effect of laboratory interactions have not been conducted with AGGRENOX.

Drug-lifestyle interactions

Pharmacokinetic studies to determine the effect of lifestyle have not been conducted with AGGRENOX.

DOSAGE AND ADMINISTRATION

Dosing Considerations

For oral administration.

Recommended Dose and Dosage Adjustment

The recommended dose of AGGRENOX is one capsule twice daily, one in the morning and one in the evening, with or without food.

Administration

The capsules should be swallowed whole without chewing.

OVERDOSAGE

Because of the dose ratio of dipyridamole to ASA, overdosage of AGGRENOX is likely to be dominated by signs and symptoms of dipyridamole overdose. For real or suspected overdose, a Poison Control Center should be contacted immediately. Careful medical management is essential.

DIPYRIDAMOLE

SYMPTOMS

Based upon the known hemodynamic effects of dipyridamole, symptoms such as feeling warm, flushes, sweating, restlessness, feeling of weakness and dizziness may occur. A drop in blood pressure and tachycardia might also be observed.

TREATMENT

Symptomatic treatment is recommended, possibly including a vasopressor drug. Gastric lavage should be considered. Since dipyridamole is highly protein bound, dialysis is not likely to be of benefit.

ASA

SYMPTOMS

In mild overdosage these may include rapid and deep breathing, nausea, vomiting, vertigo, tinnitus, flushing, sweating, thirst and tachycardia. In more severe cases acid base disturbances including respiratory alkalosis and metabolic acidosis can occur. Severe cases may show fever, hemorrhage, excitement, confusion, convulsion or coma, and respiratory failure.

TREATMENT

It consists of prevention and management of acid-base and fluid and electrolyte disturbances. Renal clearance is increased by increasing urine flow and by alkaline diuresis but care must be taken in this approach not to aggravate further the metabolic acidosis that develops and the hypokalemia. Acidemia should be prevented by administration of adequate sodium containing fluids and sodium bicarbonate. Hypoglycemia is an occasional accompaniment of salicylate overdosage and can be managed by administration of glucose solutions. If a hemorrhagic diathesis is evident, give vitamin K. Haemodialysis may be useful in complex acid base disturbances particularly in the presence of abnormal renal function.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Blood platelets participate actively in the pathogenesis of atherosclerotic lesions and thrombosis which is the principle cause of most strokes and transient ischemic attacks (TIAs). Platelets are believed to adhere to denuded, dysfunctional endothelium and to release mitogenic substances, such as platelet-derived growth factor (PDGF), that foster the lesion's progression to rupture and thrombosis. The antithrombotic action of AGGRENOX is the result of the additive antiplatelet effects of dipyridamole and acetylsalicylic acid (ASA).

DIPYRIDAMOLE

Dipyridamole inhibits the uptake of adenosine into platelets, endothelial cells and erythrocytes in vitro and in vivo; the inhibition occurs in a dose dependent manner at therapeutic plasma concentrations (0.5-1.9 µg/mL). This inhibition results in an increase in local concentrations of adenosine which acts on the platelet A2-receptor thereby stimulating platelet adenylate cyclase and increasing platelet cyclic-3', 5'-adenosine monophosphate (cAMP) levels. Via this mechanism, platelet aggregation is inhibited in response to various stimuli such as platelet activating factor (PAF), collagen and adenosine diphosphate (ADP). Reduced platelet aggregation reduces platelet consumption towards normal levels.

Dipyridamole also inhibits phosphodiesterase (PDE) in various tissues. While the inhibition of cAMP-PDE is weak, therapeutic levels of dipyridamole inhibit cyclic-3', 5'-guanosine monophosphate-PDE (cGMP-PDE), thereby augmenting the increase in cGMP produced by EDRF (endothelium-derived relaxing factor, now identified as nitric oxide).

ASA

ASA inhibits platelet aggregation by irreversible inhibition of platelet cyclo-oxygenase and thus inhibits the generation of thromboxane A2, a powerful inducer of platelet aggregation and vasoconstriction. In studies of platelet activity inhibition, 25 mg ASA was administered b.i.d. to 5 subjects for 2.5 days. Complete inhibition of collagen-induced aggregation was achieved by the 5th dose of ASA, and maximal effect persisted up to 2-3 days following stoppage of drug.s

Pharmacokinetics

There are no significant interactions between ASA and dipyridamole. The kinetics of the components are unchanged by their co-administration as AGGRENOX. AGGRENOX is not interchangeable with the individual components of ASA and dipyridamole.

DIPYRIDAMOLE

Absorption: The dissolution and absorption of dipyridamole from AGGRENOX capsules is independent of the pH of the gastrointestinal tract. Peak plasma levels are achieved in 1.5-2 hours after administration. The absolute bioavailability of dipyridamole from AGGRENOX is about 70%. With a daily maintenance dose of 400 mg of the extended release formulation, peak plasma levels at steady state are between 1.5-3 µg/mL and trough levels are between 0.4-0.8 µg/mL.

Pharmacokinetic studies to determine the effect of food have not been conducted with AGGRENOX.

Distribution: Due to its high lipophilicity, dipyridamole distributes to many organs; however it has been shown that the drug does not cross the blood brain barrier to any significant extent.

Metabolism: Dipyridamole is metabolized in the liver. In plasma, about 80% of the total amount is present as parent compound and 20% as monoglucuronide.

Excretion: Most of the glucuronide metabolite (about 95%) is excreted via bile into the feces, with some evidence of enterohepatic circulation. Renal excretion of parent compound is negligible and urinary excretion of the glucuronide metabolite is low (about 5%). The dominant half-life for elimination after oral or intravenous administration is about 40 minutes.

Special Populations and Conditions

Geriatrics: Plasma concentrations (determined as area under the curve, AUC) of dipyridamole in healthy elderly subjects (> 65 years) are about 30-50% higher than in subjects younger than 55 years, on treatment with AGGRENOX. The difference is caused mainly by reduced clearance.

Hepatic Insufficiency: Patients with mild to severe hepatic insufficiency show no change in plasma concentrations of dipyridamole compared to healthy volunteers, but show an increase in the pharmacologically inactive monoglucuronide metabolite. Dipyridamole can be dosed without restriction as long as there is no evidence of liver failure.

Renal Insufficiency: Renal excretion of dipyridamole is very low (about 5%). In patients with creatinine clearances ranging from about 15 mL/min to > 100 mL/min, no changes were observed in the pharmacokinetics of dipyridamole or its glucuronide metabolite.

ASA

Absorption: The rate of absorption of ASA from the gastrointestinal tract is dependent on the dosage form, the presence or absence of food, gastric pH, and other physiologic factors. Since ASA produces its pharmacodynamic effect via the irreversible acetylating of platelets, the time course of its pharmacodynamic activity is not dependent on the pharmacokinetics of ASA but rather on the lifespan of the platelets (approximately 8-10 days). Therefore, small differences in the pharmacokinetics of ASA, such as variations in its absorption rate or in elimination, are largely irrelevant to its pharmacologic activity with chronic administration. ASA undergoes moderate hydrolysis to salicylic acid in the liver and the gastrointestinal wall, with 50%-75% of an administered dose reaching the systemic circulation as intact ASA. Peak plasma levels of ASA are achieved 0.5-1 hour after administration of a 50 mg ASA daily dose from AGGRENOX (given as 25 mg b.i.d.). Peak mean plasma concentration at steady state is 319 ng/mL (175-463 ng/mL).

Distribution: ASA is poorly bound to plasma proteins and its apparent volume of distribution is low (10 L). At low plasma concentrations (< 100 µg/mL), approximately 90% of salicylic acid is bound to albumin. Salicylic acid is widely distributed to all tissues and fluids in the body including the central nervous system, breast milk, and fetal tissues. Early signs of salicylate overdose (salicylism), including tinnitus (ringing in the ears), occur at plasma concentrations approximating 200 µg/mL. (See ADVERSE REACTIONS; OVERDOSAGE)

Metabolism: ASA is rapidly hydrolyzed in plasma to salicylic acid, with a half-life of 15-30 minutes. Plasma levels of ASA are essentially undetectable 1-2 hours after dosing and peak salicylic acid concentrations occur within 1-2 hours of administration of ASA. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (10-20 g), the plasma half-life may be increased to over 20 hours.

Excretion: The elimination of salicylic acid follows first order kinetics at lower doses, with a resultant half-life of approximately 2-3 hours. Renal excretion of unchanged drug depends upon urinary pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from < 5% to > 80%. Alkalinization of the urine is a key concept in the management of salicylate overdose. (See OVERDOSAGE) Following therapeutic doses, about 10% is excreted as salicylic acid and 75% as salicyluric acid, in urine.

Special Populations and Conditions

Hepatic Insufficiency: Due to the ASA component, AGGRENOX is to be avoided in patients with severe hepatic insufficiency.

Renal Insufficiency: Due to the ASA component, AGGRENOX is to be avoided in patients with severe renal failure (glomerular filtration rate less than 10 mL/min).

STORAGE AND STABILITY

Store at 15 to 30°C.

SPECIAL HANDLING INSTRUCTIONS

Protect from excessive moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each hard gelatine capsule contains 200 mg dipyridamole as extended release pellets (a mixture of two release rate pellets), and 25 mg ASA as an immediate release sugar coated tablet.

AGGRENOX is available as a hard gelatine capsule, with a red cap and an ivory-coloured body, containing yellow extended release pellets incorporating dipyridamole and a round white tablet incorporating immediate-release ASA. The capsule body is imprinted in red with the Boehringer Ingelheim logo and with "01A".

Non-medicinal ingredients (in alphabetical order): acacia, aluminium stearate, colloidal silicon dioxide, corn starch, dimethicone, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, lactose monohydrate, methacrylic acid copolymer, microcrystalline cellulose, povidone, stearic acid, sucrose, talc, tartaric acid, titanium dioxide, and triacetin.

The capsule shell contains gelatine, red iron oxide and yellow iron oxide, titanium dioxide and water.

AGGRENOX is supplied in polypropylene tubes containing 60 capsules.

Aggrenox®

ASA /Extended Release Dipyridamole

Boehringer Ingelheim

www.boehringer-ingelheim.ca

Boehringer Ingelheim (Canada) Ltd.
5180 South Service Rd.,
Burlington, Ontario L7L 5H4

PAAB Member R&D

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October 5-7, 2008
Vancouver, British Columbia, Canada
7th North American Conference on Shaken Baby Syndrome (Abusive Head Trauma)
For information go to: www.dontshake.org

October 23-26, 2008
Athens, Greece
Controversies in Neurology (CONy)
For additional information regarding CONy, please visit our website: www.comtecmed.com/cony

November 5-7, 2008
Ottawa, Ontario, Canada
DIA's 6th Canadian Annual Meeting: Benefits and Risk Management: An Evolution in Progress
To register contact: Joanne Wallace (215) 442-6180, email joanne.wallace@diahome.org or visit our website www.diahome.org

November 6-7, 2008
Phoenix, Arizona, USA
Adding, Updating, and Expanding Stroke Programs and Service Lines
For more information please visit www.acius.net

November 9-11, 2008
Houston, Texas, USA
Goodman Oral Board Preparation: Neurosurgery Review by Case Management
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November 13-15, 2008
Sicily, Italy
European Charcot Foundation Symposium 2008. Multiple Sclerosis and Gender
Programme and more information available via www.charcot-ms.eu

November 16-18, 2008
Valencia, Spain
International symposium on rare diseases - Inherited Neuromuscular Diseases: Translation from Pathomechanisms to Therapies
To register go to www.fundacioncac.es/catedrasg

February 16-17, 2009
Tel Aviv, Israel
5th Annual Update Symposium on Clinical Neurology and Neurophysiology
For more information, please visit our website at: www.neurophysiology-symposium.com

March 11-15, 2009
Prague, Czech Republic
9th International Conference - Alzheimer's & Paarkinson's Diseases: Advances, Concepts & New Challenges
For more information or to register, please visit www.kenes.com/adpd

April 15-18, 2009
Rotterdam, The Netherlands
9th European Skull Base Society Meeting
For more information, please visit our website at: www.esbs2009.eu

April 25-28, 2009
Rome, Italy
XI International Facial Nerve Symposium
For more information go to www.facialnerve2009.org

April 25 - May 2, 2009
Seattle, Washington, USA
AAN Annual Meeting
For information go to: www.aan.com

May 7-9, 2009
Vancouver, British Columbia, Canada
International Vocational Outcomes in Traumatic Brain Injury Conference 2009
For information go to: www.tbicvancouver.com

June 9-12, 2009
Halifax, Nova Scotia, Canada
44th Annual Congress of the Canadian Neurological Sciences Federation
For more information go to: www.cnsfederation.org or contact the secretariat office at (403) 229-9544.

August 27-30, 2009
Munich, Germany
1st International Congress on Clinical Neuroepidemiology
For more information about the Congress. please visit our website www.neuro2009.com

August 30-September 4, 2009
Boston, Massachusetts, USA
XIV Congress of the World Federation of Neurosurgical Societies (WFNS)
For more information or to register, please visit www.AANS.org/wfns2009 or email wfns2009@aans.org

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MICARDIS® (telmisartan)

40 mg and 80 mg Tablets
THERAPEUTIC CLASSIFICATION:
Angiotensin II AT_1 Receptor Blocker

INDICATIONS AND CLINICAL USE

MICARDIS® (telmisartan) is indicated for the treatment of mild to moderate essential hypertension.
MICARDIS® may be used alone or in combination with thiazide diuretics.
The safety and efficacy of concurrent use with angiotensin converting enzyme inhibitors have not been established. Information on the use of telmisartan in combination with beta blockers is not available.

CONTRAINDICATIONS

MICARDIS® (telmisartan) is contraindicated in patients who are hypersensitive to any components of this product (see Composition).

WARNINGS

Pregnancy:
Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and mortality when administered to pregnant women. If pregnancy is detected, MICARDIS® (telmisartan) should be discontinued as soon as possible. The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and nonnatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of MICARDIS® as soon as possible unless it is considered life-saving for the mother. Rarely, probably less often than once in every thousand pregnancies, no alternative to an angiotensin II AT_1 receptor antagonist will be found. In these rare cases, the physician should apprise mothers of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra amniotic environment. If oligohydramnios is observed, contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Infants with histories of in utero exposure to an angiotensin II AT_1 receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion may be required as a means of reversing hypertension and/or substituting for disordered renal function. Telmisartan is not removed from plasma by hemodialysis. No teratogenic effects were observed when telmisartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses of up to 45 mg/kg/day with saline supplementation. In rabbits, fetotoxicity (total resorptions) associated with maternal toxicity (reduced body weight gain, mortality) was observed at the highest dose level (45 mg/kg/day). In rats, maternally toxic (reduction in body weight gain and food consumption) telmisartan doses of 50 mg/kg/day in late gestation and during lactation were observed to produce adverse effects in rat fetuses and neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain. Significant levels of telmisartan were present in rat milk and rat fetuses' blood during late gestation.

Hypotension:
In patients who are volume-depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea or vomiting, symptomatic hypotension may occur after initiation of therapy with MICARDIS®. These conditions should be corrected prior to administration of MICARDIS®. In these patients, because of the potential fall in blood pressure, therapy should be started under close medical supervision. Similar considerations apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident.

PRECAUTIONS

General:
Hepatic Impairment: As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency have reduced clearance of telmisartan. Three-to four-fold increases in C_{max} and AUC were observed in patients with liver impairment as compared to healthy subjects. MICARDIS® (telmisartan) should be used with caution in these patients (see DOSAGE AND ADMINISTRATION).
Renal Impairment: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely acute renal failure and/or death. There is no experience with long-term use of MICARDIS® (telmisartan) in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated. In susceptible patients, concomitant diuretic use may further increase the risk. Use of telmisartan should include appropriate assessment of renal function in these types of patients.
Valvular Stenosis: There is concern on theoretical grounds that patients with aortic stenosis might be at a particular risk of decreased coronary perfusion, because they do not develop as much afterload reduction.
Hyperkalemia: Drugs such as MICARDIS® that affect the renin-angiotensin-aldosterone system can cause hyperkalemia. Monitoring of serum potassium in patients at risk is recommended. Based on experience with the use of other drugs that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase the potassium level (heparin, etc.) may lead to a greater risk of an increase in serum potassium.
Use in Nursing Mothers: It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
Use in Children: Safety and effectiveness in pediatric patients have not been established.
Use in the Elderly: Of the total number of patients receiving MICARDIS® (telmisartan) in clinical studies, 551 (18.6%) were 65 to 74 years of age and 130 (4.4%) were 75 years or older. No overall age-related differences were seen in the adverse effect profile, but greater sensitivity in some older patients cannot be ruled out.
Effects on Ability to Drive and Use Machines: No studies on the effect on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery, it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy.

Drug Interactions:
Warfarin: MICARDIS® (telmisartan) administered for 10 days slightly decreased the mean warfarin trough plasma concentration; this decrease did not result in a change in International Normalized Ratio (INR). Coadministration of MICARDIS® also did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, hydrochlorothiazide or ibuprofen. For digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. It is recommended that digoxin plasma levels be monitored when initiating, adjusting or discontinuing MICARDIS®.
Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Very rare cases have also been reported with angiotensin II receptor antagonists. Therefore, serum lithium level monitoring is advisable during concomitant use.

ADVERSE EVENTS

MICARDIS® (telmisartan) has been evaluated for safety in 27 clinical trials involving 7,968 patients. Of these 7,968 patients, 5,788 patients were treated with MICARDIS® monotherapy including 1,058 patients treated for ≥1 year and 1,395 patients treated in placebo-controlled trials. In 3,400 patients, discontinuation of therapy due to adverse events was required in 2.8% of MICARDIS® patients and 6.1% placebo patients. The following potentially serious adverse reactions have been reported rarely with telmisartan in controlled clinical trials: syncope and hypotension. In placebo-controlled trials, no serious adverse event was reported with a frequency of greater that 0.1% in MICARDIS®-treated patients.

ALL CLINICAL TRIALS

The adverse drug events listed below have been accumulated from 27 clinical trials including 5,788 hypertensive patients treated with telmisartan. Adverse events have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100, >1/10); uncommon (≥1/1.000, <1/100); rare (≥1/10.000, <1/1.000); very rare (<1/10.000).
Body as a Whole, General: Common: Back pain (e.g. sciatica), chest pain, influenza-like symptoms, symptoms of infection (e.g. urinary tract infections including cystitis), fatigue, conjunctivitis. Uncommon: Abnormal vision, sweating increased.
Cardiovascular System: Common: Edema, palpitation.
Central and Peripheral Nervous System: Very common: Headache. Common: Dizziness, insomnia. Uncommon: Vertigo.
Gastro-Intestinal System: Common: Abdominal pain, diarrhea, dyspepsia, nausea, constipation, gastritis. Uncommon: Dry mouth, flatulence.
Musculo-Skeletal System: Common: Arthralgia, cramps in legs or leg pain, myalgia, arthritis, arthrosis. Uncommon: Tendinitis like symptoms.
Psychiatric System: Common: Anxiety, depression, nervousness.
Respiratory System: Common: Upper respiratory tract infections including pharyngitis and sinusitis, bronchitis, coughing, dyspnea, rhinitis.
Skin and Appendages Systems: Common: Skin disorders like eczema, rash.

CLINICAL LABORATORY FINDINGS

Hemoglobin: Infrequently, a decrease in hemoglobin has been observed which occurs more often during treatment with telmisartan than with placebo.

PLACEBO-CONTROLLED TRIALS

The overall incidence of adverse events reported with MICARDIS® (41.4%) was usually comparable to placebo (43.9%) in placebo-controlled trials. Adverse events occurring in 1% or more of 1,395 hypertensive patients treated with MICARDIS® monotherapy in placebo-controlled clinical trials, regardless of drug relationship, include the following:

Adverse Event, by System	MICARDIS® Total n=1,395 %	Placebo n=583 %
Body as a Whole		
Back pain	2.7	0.9
Chest pain	1.3	1.2
Fatigue	3.2	3.3
Influenza-like symptoms	1.7	1.5
Pain	3.5	4.3
Central & Peripheral Nervous System		
Dizziness	3.6	4.6
Headache	8.0	15.6
Somnolence	0.4	1.0
Gastrointestinal System		
Diarrhea	2.6	1.0
Dyspepsia	1.6	1.2
Nausea	1.1	1.4
Vomiting	0.4	1.0
Musculoskeletal System		
Myalgia	1.1	0.7
Respiratory System		
Coughing	1.6	1.7
Pharyngitis	1.1	0.3
Sinusitis	2.2	1.9
Upper respiratory tract infection	6.5	4.6
Heart Rate and Rhythm Disorders		
ECG abnormal specific	0.2	1.0
Palpitation	0.6	1.0
Cardiovascular Disorders, General		
Hypertension	1.0	1.7
Oedema peripheral	1.0	1.2

The incidence of adverse events was not dose-related and did not correlate with the gender, age, or race of patients.
In addition, the following adverse events, with no established causality, were reported at an incidence of <1% in placebo-controlled clinical trials.
Autonomic Nervous Systems Disorders: sweating increased.
Body as a Whole: abdomen enlarged, allergy, cyst nos, fall, fever, leg pain, rigors, syncope.
Cardiovascular Disorders, General: hypotension, hypotension-postural, leg edema.
Central & Peripheral Nervous System Disorders: hypertonia, migraine-aggravated, muscle contraction-involuntary.
Gastrointestinal System Disorders: anorexia, appetite increased, flatulence, gastrointestinal disorder nos, gastroenteritis, gastroesophageal reflux, melena, mouth dry, abdominal pain.
Heart Rate & Rhythm Disorders: arrhythmia, tachycardia.
Metabolic & Nutritional Disorders: *diabetes mellitus, hypokalemia.*
Musculoskeletal System Disorders: arthritis, arthritis aggravated, arthrosis, bursitis, fascitis plantar, tendinitis.
Myo Endo Pericardial & Valve Disorders: myocardial infarction.
Psychiatric Disorders: nervousness.
Red Blood Cell Disorders: anemia.
Reproductive Disorders, Female: vaginitis.
Resistance Mechanism Disorders: abscess, infection, bacterial, moniliasis genital, otitis media.
Respiratory System Disorders: bronchospasm, epistaxis, pneumonia, bronchitis.
Skin & Appendage Disorders: rash, skin dry.
Urinary System Disorders: dysuria, hematuria, micturition disorder, urinary tract infection.
Vascular (Extracardiac) Disorders: cerebrovascular disorder, purpura.
Vision Disorders: vision abnormal.
Clinical Laboratory Findings:
In placebo-controlled clinical trials involving 1,041 patients treated with MICARDIS® monotherapy, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of MICARDIS®.
Creatinine, Blood Urea Nitrogen: Increases in BUN (≥11.2 mg/dL) and creatinine (≥0.5 mg/dL) were observed in 1.5% and 0.6% of MICARDIS®-treated patients; the corresponding incidence was 0.3% each for placebo-treated patients. These increases occurred primarily with MICARDIS® in combination with hydrochlorothiazide. One telmisartan-treated patient discontinued therapy due to increases in creatinine and blood urea nitrogen.
Hemoglobin, Hematocrit: Clinically significant changes in hemoglobin and hematocrit (<10 mg/dL and <30% respectively) were rarely observed with MICARDIS® treatment and did not differ from rates in placebo-treated patients. No patients discontinued therapy due to anemia.
Serum Uric Acid: An increase in serum uric acid (≥2.7 mg/dL) was reported in 1.7% of patients treated with MICARDIS® and in 0.0% of patients treated with placebo. Clinically significant hyperuricemia (≥10 mEg/L) was observed in 2.3% of patients with MICARDIS® with 0.4% reported in patients at baseline. Increases in serum acid were primarily observed in patients who received MICARDIS® in combination with hydrochlorothiazide. No patient was discontinued from treatment due to hyperuricemia.
Liver Function Tests: Clinically significant elevations in AST and ALT (>3 times the upper limit of normal) occurred in 0.1% and 0.5% respectively of patients treated with MICARDIS® compared to 0.8% and 1.7% of patients receiving placebo. No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.
Serum Potassium: Marked laboratory changes in serum potassium (≥+/-1.4 mEg/L) occurred rarely and with a lower frequency in MICARDIS®-treated patients (0.3%, 0.1%, respectively) than in placebo patients (0.6%, 0.3%, respectively). Clinically significant changes in potassium (that exceed 3 mEg/L were found in 0.6% of MICARDIS®-treated patients, with 0.5% of these reported at baseline. The corresponding rates for placebo-treated patients were 0.6% and 0.8%.
Cholesterol: In placebo-controlled trials, marked increases in serum cholesterol were reported in a total of 6 telmisartan-treated patients (0.4%) and no placebo patients. Two of these patients were followed over time; in both cases cholesterol values reverted to baseline levels. Serum elevations in cholesterol were reported as adverse events in 11 of 3,445 patients (0.3%) in all clinical trials. There were no reported cases of hypercholesterolemia in telmisartan-treated patients in placebo-controlled trials.

POST-MARKETING EXPERIENCE

Since the introduction of telmisartan in the market, cases of erythema, pruritus, faintness, insomnia, depression, stomach upset, vomiting, hypotension, bradycardia, tachycardia, dyspnoea, eosinophilia, thrombocytopenia, weakness and lack of efficacy have been reported rarely. As with other angiotensin II antagonists rare cases of angio-oedema, pruritis, rash and urticaria have been reported.
Cases of muscle pain, muscle weakness, myositis and rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Limited data are available with regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and/or tachycardia. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

DOSAGE AND ADMINISTRATION

The recommended dose of MICARDIS® (telmisartan) is 80 mg once daily.
The antihypertensive effect is present within 2 weeks and maximal reduction is generally attained after four weeks. If additional blood pressure reduction is required, a thiazide diuretic may be added.
No initial dosing adjustment is necessary for elderly patients or for patients with renal impairment, but greater sensitivity in some older individuals cannot be ruled out. Markedly reduced telmisartan plasma levels were observed in patients on hemodialysis.
For patients with hepatic impairment, a starting dose of 40 mg is recommended (see PRECAUTIONS, Hepatic Impairment). MICARDIS® should be taken consistently with or without food.
Composition:
MICARDIS® Tablets contain the following inactive ingredients: sodium hydroxide, meglumine, povidone, sorbitol, and magnesium stearate.
Stability and Storage Recommendations:
MICARDIS® Tablets are hygroscopic and require protection from moisture. Tablets are packaged in blisters and should be stored at room temperature, 15 to 30°C (59-86°F).
Tablets should not be removed from blisters until immediately prior to administration.

AVAILABILITY OF DOSAGE FORMS

MICARDIS® is available as white, oblong-shaped, uncoated tablets containing telmisartan 40 mg or 80 mg. Tablets are marked with the Boehringer Ingelheim logo on one side, and on the other side, with a decorative score and either 51H or 52H for the 40 mg and 80 mg strengths, respectively.
MICARDIS® Tablets 40 mg are individually blister sealed in cartons of 28 tablets as 4 cards containing 7 tablets each.
MICARDIS® Tablets 80 mg are individually blister sealed in cartons of 28 tablets as 4 cards containing 7 tablets each.

Product Monograph available upon request.

References:

1. Mallion JM *et al.* ABPM Comparison of the Antihypertensive Profiles of the Selective Angiotensin II Receptor Antagonists Telmisartan and Losartan in Patients With Mild-to-Moderate Hypertension. *Journal of Human Hypertension* 1999;13(10):657-664. **2.** Lacourcière Y, *et al.* A Multicenter, 14-Week Study of Telmisartan and Ramipril in Patients With Mild-to-Moderate Hypertension Using Ambulatory Blood Pressure Monitoring. *American Journal of Hypertension* 2006;19:104-112. **3.** MICARDIS® Product Monograph, Boehringer Ingelheim (Canada) Ltd. October 2005. **4.** Cozaar® Product Monograph, E.I. du Pont de Nemours and Company. **5.** Diovan® Product Monograph, Novartis. **6.** Avapro™ Product Monograph (Canada), Sanofi-Synthelabo. **7.** Atacand® Product Monograph, AstraZeneca Pharma Inc. **8.** Teveten® Product Monograph, Solvay Pharma Inc.

MICARDIS®
TELMISARTAN 80mg AT_1 RECEPTOR BLOCKER
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Once-a-day

Aricept®

donepezil HCl 5 & 10 mg tablets

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Cholinesterase inhibitor

INDICATIONS AND CLINICAL USE

ARICEPT (donepezil hydrochloride) is indicated for the symptomatic treatment of patients with mild, moderate and severe dementia of the Alzheimer's type.

Efficacy of **ARICEPT** in patients with mild-to-moderate Alzheimer's disease (AD) was established in two 24-week and one 54-week placebo-controlled trials. Efficacy in patients with severe AD was established in two 24-week/6-month placebo-controlled trials.

ARICEPT tablets should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of AD.

CONTRAINDICATIONS

ARICEPT (donepezil hydrochloride) is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives.

SPECIAL POPULATIONS

Use in pregnant or nursing women

The safety of **ARICEPT** during pregnancy and lactation has not been established and therefore, it should not be used in women of childbearing potential or in nursing mothers unless, in the opinion of the physician, the potential benefits to the patient outweigh the possible hazards to the fetus or the infant.

Use in children

There are no adequate and well-controlled trials to document the safety and efficacy of **ARICEPT** in any illness occurring in children. Therefore, **ARICEPT** is not recommended for use in children.

Use in elderly patients (≥65 years of age)

In AD patients, nausea, diarrhea, vomiting, insomnia, fatigue and anorexia increased with dose and age, and the incidence appeared to be greater in female patients. Since cholinesterase inhibitors as well as AD can be associated with significant weight loss, caution is advised regarding the use of **ARICEPT** in low body weight elderly patients, especially in those ≥85 years old.

Use in elderly patients with comorbid disease

There is limited safety information for **ARICEPT** in patients with mild-to-moderate or severe AD and significant comorbidity. The use of **ARICEPT** in AD patients with chronic illnesses common among the geriatric population should be considered only after careful risk/benefit assessment and include close monitoring for adverse events (AEs). Caution is advised regarding the use of **ARICEPT** doses above 5 mg in this patient population.

In severe AD, the possibility of comorbid vascular disease and risk factors for vascular AEs and mortality should be considered.

Use in patients with vascular dementia

Three clinical trials, each of 6 months duration, were conducted to evaluate the safety and efficacy of **ARICEPT** for the symptomatic treatment of individuals meeting the NINDS-AIREN criteria for probable or possible vascular dementia (VaD). The NINDS-AIREN criteria are designed to identify patients with dementia that appears to be due solely to vascular causes, and to exclude patients with AD. **ARICEPT** was not shown to be an effective treatment for patients with VaD in 2 of these clinical trials.

The safety profile from these controlled clinical trials in VaD patients indicates that the rate of occurrence of treatment-emergent AEs overall was higher in VaD patients (86%) than in AD patients (75%). This was seen in both **ARICEPT**-treated subjects and placebo-treated subjects, and may relate to the greater number of comorbid medical conditions in the VaD population. In 2 of the clinical trials, there was a higher rate of mortality among patients treated with **ARICEPT**, during double-blind treatment; this result was statistically significant for 1 of these 2 trials. For the 3 VaD studies combined, the mortality rate in the **ARICEPT** group (1.7%, 25/1,475) was numerically higher than in the placebo group (1.1%, 8/718), but this difference was not statistically significant (see **Supplemental Product Information** below).

There is no evidence of an increased risk of mortality when **ARICEPT** is used in patients with mild-to-moderate AD.

Safety Information

WARNINGS AND PRECAUTIONS

Cardiovascular

Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate (e.g., bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions. In clinical trials in AD, most patients with serious cardiovascular conditions were excluded. Patients, such as those with controlled hypertension (DBP<95 mmHg), right bundle branch blockage, and pacemakers, were included. Therefore, caution should be taken in treating patients with active coronary artery disease and congestive heart failure. Syncopal episodes have been reported in association with the use of **ARICEPT**. It is recommended that **ARICEPT** should not be used in patients with cardiac conduction abnormalities (except for right bundle branch block) including "sick sinus syndrome" and those with unexplained syncopal episodes.

Gastrointestinal

Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs) including high doses of acetylsalicylic acid (ASA), should be monitored for symptoms of active or occult gastrointestinal bleeding. Clinical studies of **ARICEPT** have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding (see **ADVERSE REACTIONS** section).

ARICEPT, as a predictable consequence of its pharmacological properties, has been shown to produce, in controlled clinical trials in patients with AD, diarrhea, nausea and vomiting. These effects, when they occur, appear more frequently with the 10 mg dose than with the 5 mg dose. In most cases, these effects have usually been mild and transient, sometimes lasting 1 to 3 weeks and have resolved during continued use of **ARICEPT** (see **ADVERSE REACTIONS** section). Treatment with the 5 mg/day dose for 4-6 weeks prior to increasing the dose to 10 mg/day is associated with a lower incidence of gastrointestinal intolerance.

Genitourinary

Although not observed in clinical trials of **ARICEPT**, cholinomimetics may cause bladder outflow obstruction.

Hepatic

There is limited information regarding the pharmacokinetics of **ARICEPT** in hepatically-impaired AD patients.

Close monitoring for AEs in patients with hepatic disease being treated with **ARICEPT** is therefore recommended.

Neurologic

Seizures: Some cases of seizures have been reported with the use of **ARICEPT** in clinical trials and from spontaneous Adverse Reaction reporting. Cholinomimetics can cause a reduction of seizure threshold, increasing the risk of seizures. However, seizure activity may also be a manifestation of AD. The risk/benefit of **ARICEPT** treatment for patients with a history of seizure disorder must therefore be carefully evaluated.

ARICEPT has not been studied in patients with Parkinsonian features. The efficacy and safety of **ARICEPT** in these patients are unknown.

Peri-operative considerations

Anesthesia: ARICEPT, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

Renal

There is limited information regarding the pharmacokinetics of **ARICEPT** in renally-impaired AD patients.

Close monitoring for AEs in patients with renal disease being treated with **ARICEPT** is therefore recommended.

Respiratory

Because of their cholinomimetic action, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. **ARICEPT** has not been studied in patients under treatment for these conditions and should therefore be used with particular caution in such patients.

ADVERSE REACTION SERIOUSNESS AND INCIDENCE

Mild-to-moderate Alzheimer's disease

A total of 747 patients with mild-to-moderate AD were treated in controlled clinical studies with **ARICEPT** (donepezil hydrochloride). Of these patients, 613 (82%) completed the studies. The mean duration of treatment for all **ARICEPT** groups was 132 days (range 1-356 days). The rates of discontinuation from controlled clinical trials of **ARICEPT** due to AEs for the **ARICEPT** 5 mg/day treatment groups were comparable to those of placebo-treatment groups at approximately 5%. The rate of discontinuation of patients who received the 10 mg/day dose after only a 1-week initial treatment with 5 mg/day **ARICEPT** was higher at 13% (see Table 1). The most common AEs, defined as those occurring at a frequency of at least 5% in patients

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receiving 10 mg/day and twice the placebo rate, are largely predicted by **ARICEPT**'s cholinomimetic effects. These include nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue and anorexia.

These AEs were often of mild intensity and transient, resolving during continued **ARICEPT** treatment without the need for dose modification.

There is evidence to suggest that the frequency of these common AEs may be affected by the duration of treatment with an initial 5 mg daily dose prior to increasing the dose to 10 mg/day (see Table 2 and **Supplemental Product Information** below).

Severe Alzheimer's disease

A total of 573 patients with severe AD were treated in controlled clinical studies with **ARICEPT**. Of these patients, 441 (77%) completed the studies. The duration of double-blind treatment in all studies was 24 weeks. The mean duration of treatment for all **ARICEPT** groups was 148.4 days (range 1-231 days). The mean daily dose of **ARICEPT** was 7.5 mg/day.

In clinical trials of patients with severe AD, most patients with significant comorbid conditions were excluded. The use of **ARICEPT** in AD patients with chronic illnesses common among the geriatric population should be considered only after careful risk/benefit assessment and should include close monitoring for AEs.

In controlled clinical trials in severe AD, the rate of discontinuation due to AEs was 11.3% in patients treated with **ARICEPT**, compared to 6.7% in the placebo group. The most common AEs that led to discontinuation, more often in patients treated with **ARICEPT** than placebo, were diarrhea, nausea, vomiting, urinary tract infection, decreased appetite, and aggression. Each of these AEs led to discontinuation of less than 2% of patients treated with **ARICEPT**.

The incidence profile for AEs for severe AD was similar to that of mild-to-moderate AD (see Table 4).

The most common AEs, defined as those occurring at a frequency of at least 5% in patients and twice the placebo rate, were vomiting, diarrhea, nausea, and aggression. Overall, the majority of AEs were judged by the investigators to be mild or moderate in intensity.

Results from the controlled clinical trials indicate that the incidence of AEs, such as vomiting, urinary tract infection, urinary incontinence, pneumonia, falls, decreased appetite, aggression, restlessness, hallucination and confusion, may be higher in **ARICEPT**- and placebo-treated patients with severe AD than in patients with mild-to-moderate AD.

Postmarket adverse drug reactions

Voluntary reports of AEs temporally associated with **ARICEPT** that have been received since market introduction that are not listed above, and for which there is inadequate data to determine the causal relationship with the drug, include the following: abdominal pain, cholecystitis, convulsions, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, pancreatitis, and rash.

DRUG INTERACTIONS

Concomitant use with other drugs

Use with anticholinergics: Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

Use with cholinomimetics and other cholinesterase inhibitors: A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists, such as bethanechol.

Use with other psychoactive drugs: Few patients in controlled clinical trials received neuroleptics, antidepressants or anticonvulsants. There is thus limited information concerning the interaction of **ARICEPT** with these drugs.

Drug-drug interactions

Pharmacokinetic studies, limited to short-term, single-dose studies in young subjects, evaluated the potential of **ARICEPT** for interaction with theophylline, cimetidine, warfarin and digoxin administration. No significant effects on the pharmacokinetics of these drugs were observed. Similar studies in elderly patients were not done (see **Supplemental Product Information** below).

Health Canada may be notified by phone of serious or unexpected reaction to this drug at: 1-866-234-2345.

Administration

Dosing considerations

ARICEPT (donepezil hydrochloride) or **ARICEPT RDT** should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of AD.

Special populations: The use of **ARICEPT** in AD patients with chronic illnesses common among the geriatric population should be considered only after careful risk/benefit assessment and include close monitoring for AEs. It is recommended that **ARICEPT** be used with caution in these patient populations. AEs are more common in individuals of low body weight, in patients ≥85 years old and in females.

Recommended dose and dosage adjustment

Adults: The recommended initial dose of **ARICEPT** or **ARICEPT RDT** is 5 mg taken once daily. Therapy with the 5 mg dose should be maintained for 4-6 weeks before considering a dose increase, in order to avoid or decrease the incidence of the most common adverse reactions to the drug (see **ADVERSE REACTIONS** section) and to allow plasma levels to reach steady state.

Based on clinical judgement, the 10 mg daily dose may be considered following 4-6 weeks of treatment at 5 mg/day. The maximum recommended dose is 10 mg taken once daily.

Following initiation of therapy or any dosage increase, patients should be closely monitored for AEs.

Special populations: AEs are more common in individuals of low body weight, in patients ≥85 years old and in females. In elderly women of low body weight, the dose should not exceed 5 mg/day.

In a population of cognitively-impaired individuals, safe use of this and all other medications may require supervision.

Administration

ARICEPT should be taken once daily in the morning or evening. It may be taken with or without food.

ARICEPT tablets should be swallowed whole with water.

ARICEPT RDT should be placed on the tongue and allowed to disintegrate before swallowing with water.

Supplemental Product Information

WARNINGS AND PRECAUTIONS

Use in pregnant and nursing women

Teratology studies conducted in pregnant rats at doses of up to 16 mg/kg/day and in pregnant rabbits at doses of up to 10 mg/kg/day did not disclose any evidence for a teratogenic potential of **ARICEPT**.

Use in elderly patients (≥65 years of age)

In controlled clinical studies with 5 and 10 mg **ARICEPT** in patients with mild-to-moderate AD, there were 536 patients between the ages of 65 to 84, and 37 patients aged ≥85 years treated with **ARICEPT**. In controlled clinical trials of patients with severe AD, there were 158 patients who were ≤74 years of age, 276 patients between the ages of 75 and 84, and 139 patients aged ≥85 years treated with **ARICEPT**.

Use in patients with vascular dementia

Mortality rates in ARICEPT vascular dementia clinical trials

Study	Placebo	ARICEPT 5 mg	*p*-value[x]	ARICEPT 10 mg	*p*-value[x]
307	3.5% (7/199)	1.0% (2/198)	0.17	2.4% (5/206)	0.57
308	0.5% (1/193)	1.9% (4/208)	0.37	1.4% (3/215)	0.62
319	0% (0/326)	1.7% (11/648)	0.02	*	NA
Combined	1.1% (8/718)	1.7% (25/1,475)			0.35

* No 10 mg **ARICEPT** treatment arm in Study 319.

[x] *p*-values are for 5 mg donepezil vs. placebo and 10 mg donepezil vs. placebo.

The majority of deaths in patients taking either **ARICEPT** or placebo appear to have resulted from various vascular-related causes, which may be expected in this elderly, fragile, population with comorbid vascular disease. In the 3 combined VaD clinical trials, there were similar proportions of patients with serious AEs in both treatment groups (approximately 15%), and similar proportions of patients with serious cardiovascular or cerebrovascular AEs (non-fatal and fatal, approximately 8%). The proportion of patients who had a fatal cardiovascular or cerebrovascular AE was numerically higher in the **ARICEPT** group than in the placebo group, but this difference was not statistically significant across the 3 trials.

ADVERSE REACTIONS

Mild-to-moderate Alzheimer's disease

The most common AEs leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1.

Table 1. Most frequent adverse events in patients with mild-to-moderate Alzheimer's disease leading to withdrawal from controlled clinical trials by dose group

Dose group	Placebo	5 mg/day ARICEPT	10 mg/day ARICEPT
Number of patients randomized	355	350	315
Events/% discontinuing			
Nausea	1%	1%	3%
Diarrhea	0%	<1%	3%
Vomiting	<1%	<1%	2%

An open-label study was conducted with 269 patients who received placebo in the 15- and 30-week studies. These patients received a 5 mg/day dose for 6 weeks prior to initiating treatment with 10 mg/day. The rates of common AEs were lower than those seen in controlled clinical trial patients who received 10 mg/day after only a 1-week initial treatment period with a 5 mg daily dose, and were comparable to the rates noted in patients treated only with 5 mg/day.

See Table 2 for a comparison of the most common AEs following 1- and 6-week initial treatment periods with 5 mg/day **ARICEPT**.

Table 2. Comparison of rates of adverse events in patients with mild-to-moderate Alzheimer's disease treated with 10 mg/day after 1 and 6 weeks of initial treatment with 5 mg/day

	No initial treatment		1-week initial treatment *with 5 mg/day*	6-week initial treatment *with 5 mg/day*
Adverse event	**Placebo (n=315)**	**5 mg/day (n=311)**	**10 mg/day (n=315)**	**10 mg/day (n=269)**
Nausea	6%	5%	19%	6%
Diarrhea	5%	8%	15%	9%
Insomnia	6%	6%	14%	6%
Fatigue	3%	4%	8%	3%
Vomiting	3%	3%	8%	5%
Muscle cramps	2%	6%	8%	3%
Anorexia	2%	3%	7%	3%

The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behaviour, and the kinds of patients treated may differ.

Table 3 lists treatment-emergent signs and symptoms (TESS) that were reported in at least 2% of patients from placebo-controlled clinical trials who received **ARICEPT**, and for which the rate of occurrence was greater for **ARICEPT** than placebo-assigned patients. In general, AEs occurred more frequently in female patients and with advancing age.

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Table 3. Mild-to-moderate Alzheimer's disease: Adverse events reported in controlled clinical trials in at least 2% of patients receiving ARICEPT and at a higher frequency than placebo-treated patients

Body system/Adverse events	Placebo n=355	ARICEPT n=747
Percent of patients with any adverse event	**72**	**74**
Body as a whole		
Headache	9	10
Pain, various locations	8	9
Accident	6	7
Fatigue	3	5
Cardiovascular system		
Syncope	1	2
Digestive system		
Nausea	6	11
Diarrhea	5	10
Vomiting	3	5
Anorexia	2	4
Hemic and lymphatic system		
Ecchymosis	3	4
Metabolic and nutritional		
Weight decrease	1	3
Musculoskeletal system		
Muscle cramps	2	6
Arthritis	1	2
Nervous system		
Insomnia	6	9
Dizziness	6	8
Depression	<1	3
Abnormal dreams	0	3
Somnolence	<1	2
Urogenital		
Frequent urination	1	2

Other adverse events observed during clinical trials in mild-to-moderate Alzheimer's disease

During the premarketing phase, **ARICEPT** has been administered to over 1,700 individuals with mild-to-moderate AD for various lengths of time during clinical trials worldwide. Approximately 1,200 patients have been treated for at least 3 months, and more than 1,000 patients have been treated for at least 6 months. Controlled and uncontrolled trials in the United States included approximately 900 patients. In regards to the highest dose of 10 mg/day, this population includes 650 patients treated for 3 months, 475 patients treated for 6 months and 115 patients treated for over 1 year. The range of patient exposure is from 1 to 1,214 days.

Treatment-emergent signs and symptoms that occurred during 3 placebo-controlled clinical trials and 2 open-label trials of patients with mild-to-moderate AD were recorded as AEs by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the studies were integrated and the events were grouped into a smaller number of standardized categories using a modified COSTART dictionary and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 900 patients from these trials experiencing that event while receiving **ARICEPT**. All AEs occurring at least twice are included. AEs already listed in Tables 2 and 3 are not repeated here (i.e., events occurring at an incidence >2%). Also excluded are COSTART terms too general to be informative, or events less likely to be drug-caused. Events are classified by body system and listed as occurring in ≥1% and <2% of patients (i.e., in 1/100 to 2/100 patients: frequent) or in <1% of patients (i.e., in 1/100 to 1/1,000 patients: infrequent). These AEs are not necessarily related to **ARICEPT** treatment, and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Body as a whole: (≥1% and <2%) influenza, chest pain, toothache; (<1%) fever, edema face, periorbital edema, hernia hiatal, abscess, cellulitis, chills, generalized coldness, head fullness, head pressure, listlessness.

Cardiovascular system: (≥1% and <2%) hypertension, vasodilation, atrial fibrillation, hot flashes, hypotension; (<1%) angina pectoris, postural hypotension, myocardial infarction, premature ventricular contraction, arrhythmia, AV Block (1st degree), congestive heart failure, arteritis, bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thromboses.

Digestive system: (≥1% and <2%) fecal incontinence, gastrointestinal bleeding, bloating, epigastric pain; (<1%) eructation, gingivitis, increased appetite, flatulence, periodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminases, hemorrhoids, ileus, increased thirst, jaundice, melena, polydipsia, duodenal ulcer, stomach ulcer.

Endocrine system: (<1%) diabetes mellitus, goiter.

Hemic & lymphatic system: (<1%) anemia, thrombocythemia, thrombocytopenia, eosinophilia, erythrocytopenia.

Nutritional disorders: (≥1% and <2%) dehydration; (<1%) gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase.

Musculoskeletal system: (≥1% and <2%) bone fracture; (<1%) muscle weakness, muscle fasciculation.

Nervous system: (≥1% and <2%) delusions, tremor, irritability, paresthesia, aggression, vertigo, ataxia, libido increased, restlessness, abnormal crying, nervousness, aphasia; (<1%) cerebrovascular accident, intracranial hemorrhage, transient ischemic attack, emotional lability, neuralgia, coldness (localized), muscle spasm, dysphoria, gait abnormality, hypertonia, hypokinesia, neurodermatitis, numbness (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing, seizures.

Respiratory system: (≥1% and <2%) dyspnea, sore throat, bronchitis; (<1%) epistaxis, postnasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring.

Skin and appendages: (≥1% and <2%) abrasion, pruritus, diaphoresis, urticaria; (<1%) dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, hirsutism, skin striae, night sweats, skin ulcer.

Special senses: (≥1% and <2%) cataract, eye irritation, blurred vision; (<1%) dry eyes, glaucoma, earache, tinnitus, blepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjunctival hemorrhage, ear buzzing, motion sickness, spots before eyes.

Urogenital system: (≥1% and <2%) urinary incontinence, nocturia; (< 1%) dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal failure, vaginitis.

Long-term safety for mild-to-moderate Alzheimer's disease

Patients were exposed to **ARICEPT** in 2 open-label extension mild-to-moderate AD studies (n=885) of over 2 years. In 1 of the studies, 763 patients who previously completed 1 of 2 placebo-controlled studies of 15 or 30 weeks duration continued to receive **ARICEPT** and were evaluated for safety and neuropsychological evaluations for up to 152 weeks; the safety profile of **ARICEPT** in this extension study remained consistent with that observed in placebo-controlled trials. Following 1 and 2 years of treatment, 76% (n=580) and 49% (n=374) of these patients, respectively, were still receiving therapy (cumulative weeks 48 and 108).

Severe Alzheimer's disease

Table 4 lists treatment-emergent signs and symptoms (TESS) that were reported in at least 2% of patients from placebo-controlled clinical trials who received **ARICEPT**, and for which the rate of occurrence was greater for **ARICEPT** than placebo-assigned patients.

Table 4. Severe Alzheimer's disease: Adverse events reported in controlled clinical trials in at least 2% of patients receiving ARICEPT and at a higher frequency than placebo-treated patients

Body system/Adverse events	Placebo n=465	ARICEPT n=573
Percent of patients with any adverse event	**74**	**81**
Gastrointestinal		
Diarrhea	4	10
Vomiting	4	8
Nausea	3	6
Fecal incontinence	1	2
General		
Pyrexia	1	2
Chest pain	0	2
Infections and infestations		
Urinary tract infection	7	8
Nasopharyngitis	6	8
Pneumonia	3	4
Injury, poisoning, procedural complications		
Fall	9	10
Contusion	2	4
Skin laceration	1	2
Investigations		
Blood creatine phosphokinase increased	1	2
Metabolism and nutrition		
Anorexia	2	4
Decreased appetite	1	3
Dehydration	1	2
Musculoskeletal and connective tissue		
Back pain	2	3
Osteoarthritis	1	2
Nervous system		
Headache	3	5
Somnolence	0	2
Psychiatric		
Aggression	2	5
Insomnia	3	4
Restlessness	2	3
Hallucination	1	2
Confusional state	1	2
Renal and urinary		
Urinary incontinence	2	3
Respiratory		
Cough	1	2
Skin		
Eczema	1	2
Vascular		
Hypertension	1	2

A frequency of 0 has been used when frequencies were <0.5%

Other AEs that occurred with an incidence of at least 2% in **ARICEPT**-treated patients, and at an equal or lower rate than in placebo-treated patients, included: abdominal pain, fatigue, gastroenteritis, excoriation, dizziness, anxiety and depression.

Long-term safety for severe Alzheimer's disease

In Study 315, which was a 24-week, randomized, placebo-controlled study in severe AD patients, at the end of double-blind treatment, 229 patients entered open-label **ARICEPT** treatment for up to an additional 12 weeks. Therefore, at the end of the open-label phase, 111 patients had received up to 36 weeks of **ARICEPT** treatment and 118 patients had received up to 12 weeks of **ARICEPT** treatment. The most commonly affected body systems, types and frequencies of AEs reported during 12 weeks of open-label **ARICEPT** treatment were similar to what was observed during 24 weeks of double-blind treatment.

Gastrointestinal AEs (diarrhea, nausea, vomiting, anorexia) were reported at a higher frequency in patients who received up to 12 weeks of **ARICEPT** treatment. Other AEs reported at higher frequencies in patients treated with **ARICEPT** for up to 12 weeks included infection, insomnia, pneumonia, fever, dizziness, hypertension, asthenia, tremor, pharyngitis, hallucinations, convulsions and cysts.

In patients treated with **ARICEPT** for up to 36 weeks, accidental injury, urinary incontinence and urinary tract infections were reported at higher frequencies.

DRUG INTERACTIONS

Drug-drug interactions

Drugs highly bound to plasma proteins: Drug displacement studies have been performed *in vitro* between donepezil, a highly bound drug (96%) and other drugs such as furosemide, digoxin, and warfarin. Donepezil at concentrations of 0.3-10 µg/mL did not affect the binding of furosemide (5 µg/mL), digoxin (2 ng/mL) and warfarin (3 µg/mL) to human albumin. Similarly, the binding of donepezil to human albumin was not affected by furosemide, digoxin and warfarin.

Effect of ARICEPT on the metabolism of other drugs: *In vitro* studies show a low rate of donepezil binding to CYP 3A4 and CYP 2D6 isoenzymes (mean Ki about 50-130 µM), which, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interferences. In a pharmacokinetic study involving 18 healthy volunteers, the administration of **ARICEPT** at a dose of 5 mg/day for 7 days had no clinically significant effect on the pharmacokinetics of ketoconazole. No other clinical trials have been conducted to investigate the effect of **ARICEPT** on the clearance of drugs metabolized by CYP 3A4 (e.g., cisapride, terfenadine) or by CYP 2D6 (e.g., imipramine).

It is not known whether **ARICEPT** has any potential for enzyme induction.

Effect of other drugs on the metabolism of ARICEPT: Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. In a pharmacokinetic study, 18 healthy volunteers received 5 mg/day **ARICEPT** together with 200 mg/day ketoconazole for 7 days. In these volunteers, mean donepezil plasma concentrations were increased by about 30%-36%. Inducers of CYP 2D6 and CYP 3A4 (e.g., phenytoin, carbamazepine, dexamethasone, rifampin and phenobarbital) could increase the rate of elimination of **ARICEPT**.

Pharmacokinetic studies demonstrated that the metabolism of **ARICEPT** is not significantly affected by concurrent administration of digoxin or cimetidine.

Drug-food interactions

Food does not have an influence on the rate and extent of donepezil hydrochloride absorption.

Drug-herb interactions

Interactions with herbal products have not been established.

Drug-laboratory interactions

Interactions with laboratory tests have not been established.

SYMPTOMS AND TREATMENT OF OVERDOSE

Symptoms: Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

Treatment: The elimination half-life of **ARICEPT** (donepezil hydrochloride) at recommended doses is approximately 70 hours. Thus, in the case of overdose, it is anticipated that prolonged treatment and monitoring of adverse and toxic reactions will be necessary. As in any case of overdose, general supportive measures should be utilized.

Tertiary anticholinergics, such as atropine, may be used as an antidote for **ARICEPT** overdosage. Intravenous atropine sulfate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether **ARICEPT** and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration).

Dose-related signs of toxicity observed in animals included: reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, fasciculation, and lower body surface temperature.

Product Monograph available on request.

See our AD on pages A-8, A-9

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Maxalt®

rizatriptan benzoate tablets

Maxalt RPD®

rizatriptan benzoate wafers

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: 5-HT_1 Receptor Agonist

INDICATIONS AND CLINICAL USE

Adults

MAXALT® (rizatriptan benzoate) is indicated for the acute treatment of migraine attacks with or without aura in adults.

MAXALT® is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic, ophthalmoplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of MAXALT® have not been established for cluster headache, which is present in an older, predominantly male population.

Pediatrics (<18 years of age) / Geriatrics (> 65 years of age)

The safety and efficacy of MAXALT® has not been established in these age groups and its use is not recommended (see WARNINGS AND PRECAUTIONS, Special Populations in the Product Monograph).

CONTRAINDICATIONS

MAXALT® (rizatriptan benzoate) is contraindicated:

- **in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias (especially tachycardias), and in patients with other significant underlying cardiovascular diseases (e.g., atherosclerotic disease, congenital heart disease). Ischemic cardiac syndromes include, but are not restricted to, angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal's variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks (TIAs). Peripheral vascular disease includes, but is not limited to, ischemic bowel disease, or Raynaud's syndrome (see WARNINGS AND PRECAUTIONS);**
- **in patients with uncontrolled or severe hypertension (see WARNINGS AND PRECAUTIONS);**
- **within 24 hours of treatment with another 5-HT_1 agonist, or an ergotamine-containing or ergot-type medication like dihydroergotamine or methysergide;**
- **in patients with hemiplegic, ophthalmoplegic or basilar migraine;**
- **with concurrent administration of MAO inhibitors or within 2 weeks of discontinuation of MAO inhibitor therapy (see DRUG INTERACTIONS in the Supplemental Product Information section);**
- **in patients with severe hepatic impairment;**
- **in patients with known hypersensitivity.**

SPECIAL POPULATIONS

For use in special populations, see WARNINGS AND PRECAUTIONS, Special Populations.

Safety Information

WARNINGS AND PRECAUTIONS

(see Supplemental Product Information for full listing)

General

MAXALT® should only be used where a clear diagnosis of migraine has been established. For a given attack, if a patient has no response to the first dose of rizatriptan, the diagnosis of migraine should be reconsidered before administration of a second dose.

Psychomotor Effect: Dizziness, somnolence and asthenia/fatigue (see ADVERSE REACTIONS in the Supplemental Product Information section). Patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that MAXALT® does not adversely affect them.

Cardiovascular

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events:

MAXALT® has been associated with transient chest and/or neck pain and tightness which may resemble angina pectoris. Following the use of other 5-HT_1 agonists, in rare cases these symptoms have been identified as being the likely result of coronary vasospasm or myocardial ischemia. Rare cases of serious coronary events or arrhythmia have occurred following use of other 5-HT_1 agonists, and may therefore also occur with MAXALT®. Because of the potential of this class of compounds (5-$HT_{1B/1D}$ agonists) to cause coronary vasospasm, MAXALT® should not be given to patients with documented ischemic or vasospastic coronary artery disease (see CONTRAINDICATIONS). It is strongly recommended that MAXALT® not be given to patients in whom unrecognized coronary artery disease (CAD) is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is unknown. If, during the cardiovascular evaluation, the patient's medical history, electrocardiographic or other investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, MAXALT® should not be administered (see CONTRAINDICATIONS).

For patients with risk factors predictive of CAD, who are considered to have a satisfactory cardiovascular evaluation, the first dose of rizatriptan should be administered in the setting of a physician's office or similar medically staffed and equipped facility. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following MAXALT®, in these patients with risk factors. However, an absence of drug-induced cardiovascular effects on the occasion of the initial dose does not preclude the possibility of such effects occurring with subsequent administrations.

Intermittent long-term users of MAXALT® who have or acquire risk factors predictive of CAD, as described above, should receive periodic interval cardiovascular evaluation as they continue to use MAXALT®.

If symptoms consistent with angina occur after the use of MAXALT®, ECG evaluation should be carried out to look for ischemic changes.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to MAXALT®.

Discomfort in the chest, neck, throat and jaw (including pain, pressure, heaviness and tightness) has been reported after administration of rizatriptan. Because drugs in this class may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prinzmetal's variant angina before receiving additional doses of medication, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following MAXALT® administration should be evaluated for atherosclerosis or predisposition to vasospasm (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

For more information on adverse events associated with 5-HT_1 agonists see WARNINGS AND PRECAUTIONS in the Supplemental Product Information section.

Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients receiving 5-HT_1 agonists with and without a history of hypertension. In healthy young male and female subjects who received maximal doses of MAXALT® (10 mg every 2 hours for 3 doses), slight increases in blood pressure (approximately 2-3 mmHg) were observed. In patients with controlled hypertension, MAXALT® should be administered with caution, as transient increases in blood pressure and peripheral vascular resistance have been observed in a small portion of patients.

Endocrine and Metabolism

Phenylketonurics: Phenylketonuric patients should be informed that MAXALT RPD® Wafers contain phenylalanine (a component of aspartame). Each 5 mg wafer contains 1.05 mg phenylalanine, and each 10 mg wafer contains 2.10 mg phenylalanine.

Hepatic/Biliary/Pancreatic

Rizatriptan should be used with caution in patients with moderate hepatic insufficiency due to an increase in plasma concentrations of approximately 30% (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations in the Product Monograph, and DOSAGE AND ADMINISTRATION).

Neurologic

Seizures: Caution should be observed if MAXALT® is to be used in patients with a history of epilepsy or structural brain lesions which lower the convulsion threshold.

Renal

Rizatriptan should be used with caution in dialysis patients due to a decrease in the clearance of rizatriptan, resulting in approximately 44% increase in plasma concentrations (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations in the Product Monograph, and DOSAGE AND ADMINISTRATION).

Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome

Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans. If concomitant treatment with MAXALT® and SSRIs (e.g., sertraline, escitalopram oxalate, and fluoxetine) or SNRIs (e.g., venlafaxine, duloxetine) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) (see DRUG INTERACTIONS in the Supplemental Product Information section).

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women; therefore, rizatriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (see WARNING AND PRECAUTIONS, Special Populations in the Product Monograph).

Nursing Women: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when MAXALT® is administered to women who are breast-feeding. Rizatriptan is extensively excreted in rat milk, at a level of 5-fold or greater than maternal plasma levels.

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Special Disease Conditions: MAXALT® should be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations in the Product Monograph).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Serious cardiac events, including some that have been fatal, have occurred following use of 5-HT$_1$ agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

For more details on adverse drug reactions reported during clinical trials, see ADVERSE REACTIONS in the Supplemental Product Information section.

Post-Market Adverse Drug Reactions

The following additional adverse reactions have been reported very rarely and most have been reported in patients with risk factors predictive of CAD: Myocardial ischemia or infarction, cerebrovascular accident. The following adverse reactions have also been reported:

Hypersensitivity: Angioedema (e.g., facial edema, tongue swelling, pharyngeal edema), wheezing, urticaria, rash, toxic epidermal necrolysis.

Musculoskeletal: Facial pain.

Special Senses: Dysgeusia.

Nervous System: Serotonin syndrome.

To report a suspected adverse reaction, please contact Merck Frosst Canada Ltd. by:
Toll-free telephone: 1-800-567-2594
Toll-free fax: 1-877-428-8675
By regular mail:
Merck Frosst Canada Ltd.
P.O. Box 1005
Pointe-Claire – Dorval, QC H9R 4P8

Administration

DOSAGE AND ADMINISTRATION

Dosing Considerations

MAXALT® is recommended only for the acute treatment of migraine attacks and should not be used prophylactically.

Controlled trials have not established the effectiveness of a second dose if the initial dose is ineffective.

The safety of treating, on average, more than four headaches in a 30-day period has not been established.

Recommended Dose and Dosage Adjustment

The recommended single adult dose of MAXALT® Tablets and MAXALT RPD® Wafers is 5 mg. The maximum recommended single dose is 10 mg. There is evidence that the 10 mg dose may provide a greater effect than the 5 mg dose (see ACTIONS AND CLINICAL PHARMACOLOGY, Clinical Studies in the Product Monograph). The choice of dose should therefore be made on an individual basis, weighing the possible benefit of the 10 mg dose with the potential risk for increased adverse events.

For MAXALT RPD® Wafers, administration with liquid is not necessary. The wafer is packaged in a blister within an outer aluminum pouch. Patients should be instructed not to remove the blister from the outer pouch until just prior to dosing. The blister pack should then be peeled open with dry hands and the wafer placed on the tongue, where it will dissolve and be swallowed with the saliva.

Redosing: Doses should be separated by at least 2 hours; no more than a total of 20 mg (Tablets or Wafers) should be taken in any 24-hour period.

Patients receiving propranolol: A single 5 mg dose of MAXALT® should be used. In no instances should the total daily dose exceed 10 mg per day, given in two doses, separated by at least two hours (see DRUG INTERACTIONS in the Supplemental Product Information section).

Renal Impairment: If treatment is deemed advisable in hemodialysis patients with severe renal impairment (creatinine clearance <2 mL/min/1.73 m^2), the 5 mg MAXALT® Tablet or Wafer should be administered. No more than a total of 10 mg should be taken in any 24-hour period. Repeated dosing in renally impaired patients has not been evaluated.

Hepatic Impairment: If treatment is deemed advisable in the presence of moderate hepatic impairment, the 5 mg MAXALT® Tablet or Wafer should be administered. No more than a total of 10 mg should be taken in any 24-hour period. Repeated dosing in hepatically impaired patients has not been evaluated.

Patients with Hypertension: In patients with mild to moderate controlled hypertension, patients should be treated cautiously at the lowest effective dose.

Missed Dose

If a tablet is missed at its usual time, an extra dose should not be taken. The next dose should be taken as usual.

Study References

1. Data on file, Merck Frosst Canada Ltd.: MAXALT® — Product Monograph, 2007.

Supplemental Product Information

WARNINGS AND PRECAUTIONS

Cardiovascular

Cardiac Events and Fatalities Associated with 5-HT$_1$ Agonists: MAXALT® may cause coronary artery vasospasm. Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of 5-HT$_1$ agonists. Considering the extent of use of 5-HT$_1$ agonists in patients with migraine, the incidence of these events is extremely low.

Cerebrovascular Events and Fatalities Associated with 5-HT$_1$ Agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-HT$_1$ agonists; and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. Before treating migraine headaches with MAXALT® in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions.

Other Vasospasm-Related Events: 5-HT$_1$ agonists may cause vasospastic reactions other than coronary artery vasospasm. Extensive post-market experience has shown the use of another 5-HT$_1$ agonist to be associated with rare occurrences of peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea.

Immune

Rare hypersensitivity (anaphylaxis/anaphylactoid) reactions may occur in patients receiving 5-HT$_1$ agonists such as MAXALT®. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens. Owing to the possibility of cross-reactive hypersensitivity reactions, MAXALT® should not be used in patients having a history of hypersensitivity to chemically-related 5-HT$_1$ receptor agonists.

Neurologic

Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine or who experience a headache that is atypical for them. There have been rare reports where patients received 5-HT$_1$ agonists for severe headache that were subsequently shown to have been secondary to an evolving neurological lesion.

Ophthalmologic

Binding to Melanin-Containing Tissues: The propensity for rizatriptan to bind melanin has not been investigated. Based on its chemical properties, rizatriptan may bind to melanin and accumulate in melanin-rich tissue (e.g., eye) over time. This raises the possibility that rizatriptan could cause toxicity in these tissues after extended use. There were, however, no adverse ophthalmologic changes related to treatment with rizatriptan in the one-year dog toxicity study. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Monitoring and Laboratory Tests

No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with MAXALT®.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Typical 5-HT$_1$ Agonist Adverse Reactions: As with other 5-HT$_1$ agonists, MAXALT® has been associated with sensations of heaviness, pressure, tightness or pain which may be intense. These may occur in any part of the body including the chest, throat, neck, jaw and upper limb.

Acute Safety: In controlled clinical trials the most common adverse events during treatment with MAXALT® Tablets were asthenia/fatigue, somnolence, pain/pressure sensation and dizziness. These events appeared to be dose-related. In long-term extension studies where patients were allowed to treat multiple attacks for up to 1 year, 4% (59 out of 1525 patients) withdrew because of adverse experiences. Tables 1 and 2 list the adverse events regardless of drug relationship (incidence ≥ 1% and greater than placebo) after a single dose of MAXALT® Tablets and MAXALT RPD® Wafers, respectively.

MAXALT® was generally well-tolerated. Adverse experiences were typically mild in intensity and were transient. The frequencies of adverse experiences in clinical trials did not increase when up to three doses were taken within 24 hours. The incidences of adverse experiences were not affected by age, gender or use of prophylactic medications. There were insufficient data to assess the impact of race on the incidence of adverse events.

Table 1
Incidence (≥ 1% and Greater than Placebo) of Adverse Experiences After a Single Dose of MAXALT® Tablets or Placebo (Prior to Subsequent Dose) in Phase III Controlled Clinical Trials†

	% of Patients		
	Placebo	MAXALT® 5 mg	MAXALT® 10 mg
Number of Patients	627	977	1167
Symptoms of Potentially Cardiac Origin			
Upper Limb Sensations*	1.3	1.7	1.8
Chest Sensations*	1.0	1.6	3.1
Neck/Throat/Jaw Sensations*	0.6	1.4	2.5
Palpitations	0.2	0.9	1.0
Body as a Whole			
Asthenia/Fatigue	2.1	4.2	6.9
Abdominal Pain	1.0	1.7	2.2
Digestive System			
Nausea	3.5	4.1	5.7
Dry Mouth	1.3	2.6	3.0
Vomiting	2.1	1.6	2.3
Nervous System			
Dizziness	4.5	4.2	8.9
Somnolence	3.5	4.2	8.4
Headache	0.8	1.8	2.1
Paresthesia	1.0	1.5	2.9
Tremor	1.0	1.3	0.3
Insomnia	0.3	1.0	0.3
Skin and Skin Appendage			
Flushing	1.0	0.6	1.1

*The term "sensations" encompasses adverse events described as pain, discomfort, pressure, heaviness, constriction, tightness, heat/burning sensation, paresthesia, numbness, tingling, weakness and strange sensations.

†Data from Studies 022, 025, 029 and 030.

Table 2
Incidence (≥ 1% and Greater than Placebo) of Adverse Experiences After a Single Dose of MAXALT RPD® Wafers or Placebo (Prior to Subsequent Dose) in Phase III Controlled Clinical Trials†

	% of Patients		
	Placebo	MAXALT RPD® 5 mg	MAXALT RPD® 10 mg
Number of Patients	283	282	302
Symptoms of Potentially Cardiac Origin			
Chest Sensations*	0.4	1.4	1.7
Neck/throat/Jaw Sensations*	0.4	1.4	2.0
Tachycardia	1.1	1.4	0.3
Upper Limb Sensations*	0.4	0.7	2.0
Palpitations	0.4	0.4	1.0
Body as a Whole			
Asthenia/Fatigue	0.4	2.1	3.6
Digestive System			
Dry Mouth	2.1	6.4	6.0
Nausea	5.7	6.4	7.0
Dyspepsia	0.7	1.1	2.0
Acid Regurgitation	0	1.1	0.7
Salivation Increase	0	0	1.3
Musculoskeletal System			
Regional Heaviness	0	0	1.0
Nervous System			
Dizziness	3.9	6.4	8.6
Somnolence	2.8	4.3	5.3
Headache	0.7	1.8	2.0
Insomnia	0	1.4	0.7
Paresthesia	0.4	1.4	3.0
Hypesthesia	0	1.4	0.7
Mental Acuity Decreased	0	1.1	0.3
Tremor	0.7	1.1	0
Nervousness	0.4	1.1	0.7
Respiratory System			
Pharyngeal Discomfort	0	1.1	0.7
Skin and Skin Appendage			
Sweating	0.7	1.1	1.0
Special Senses			
Taste Perversion	1.1	1.4	2.3
Blurred Vision	0	0.4	1.3

*The term "sensations" encompasses adverse events described as pain, discomfort, pressure, heaviness, constriction, tightness, heat/burning sensation, paresthesia, numbness, tingling, weakness and strange sensations.

†Data from Studies 039 and 049.

Long-Term Safety: In long-term extension studies, a total of 1854 patients treated 16,150 migraine attacks with MAXALT® 5 mg Tablets and 24,043 attacks with MAXALT® 10 mg Tablets over a period of up to 1 year. In general, the types of clinical adverse experiences observed in the extension studies were similar to those observed in the acute studies. However, the incidences of most clinical adverse events were approximately 3-fold higher in extension, as expected, based on increased observation time. The most common adverse events per attack (defined as occurring at an incidence of at least 1%) for MAXALT® 5 mg and 10 mg, respectively, were as follows: nausea (3%, 4%), dizziness (2%, 2%), somnolence (2%, 4%), asthenia/fatigue (2%, 2%), headache (1%, 2%), vomiting (1%, <1%), chest pain (<1%, 1%) and paresthesia (<1%, 2%). Due to the lack of placebo controls in the extension studies, the role of MAXALT® in causation cannot be reliably determined.

Other Events Observed in Association with the Administration of MAXALT®: The frequencies of less commonly reported adverse clinical events are presented in the ADVERSE REACTIONS section of the Product Monograph. Because the reports include events observed in open studies, the role of MAXALT® in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc. limit the value of the quantitative frequency estimates provided. The adverse experience profile seen with MAXALT RPD® Wafers was similar to that seen with MAXALT® Tablets.

Drug Abuse and Dependence: Although the abuse potential of MAXALT® has not been specifically assessed, no abuse of, tolerance to, withdrawal from, or drug-seeking behavior was observed in patients who received MAXALT® in clinical trials or their extensions. The 5-HT$_{1B/1D}$ agonists, as a class, have not been associated with drug abuse.

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DRUG INTERACTIONS

Drug-Drug Interactions

Ergot-Containing Drugs: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and rizatriptan within 24 hours is contraindicated (see CONTRAINDICATIONS).

Monoamine Oxidase Inhibitors: Rizatriptan is principally metabolized via monoamine oxidase, 'A' subtype (MAO-A). In a drug interaction study, when MAXALT® 10 mg was administered to subjects (n=12) receiving concomitant therapy with the selective, reversible MAO-A inhibitor, moclobemide 150 mg t.i.d., there were mean increases in rizatriptan AUC and C_{max} of 119% and 41%, respectively; and the AUC of the active N-monodesmethyl metabolite of rizatriptan was increased more than 400%. The interaction would be expected to be greater with irreversible MAO inhibitors. Drug interaction studies were not conducted with selective MAO-B inhibitors. The specificity of MAO-B inhibitors diminishes with higher doses and varies among patients. Therefore, co-administration of rizatriptan in patients taking MAO-A or MAO-B inhibitors *is contraindicated (see CONTRAINDICATIONS).*

Nadolol/Metoprolol: In a drug interactions study, effects of multiple doses of nadolol 80 mg or metoprolol 100 mg every 12 hours on the pharmacokinetics of a single dose of 10 mg rizatriptan were evaluated in healthy subjects (n=12). No pharmacokinetic interactions were observed.

Oral Contraceptives: In a study of concurrent administration of an oral contraceptive during 6 days of administration of MAXALT® (10-30 mg/day) in healthy female volunteers (n=18), rizatriptan did not affect plasma concentrations of ethinyl estradiol or norethindrone.

Other 5-HT_1 Agonists: The administration of rizatriptan with other 5-HT_1 agonists has not been evaluated in migraine patients. Because their vasospastic effects may be additive, co-administration of rizatriptan and other 5-HT1 agonists within 24 hours of each other is contraindicated (see CONTRAINDICATIONS).

Propranolol: MAXALT® should be used with caution in patients receiving propranolol, since the pharmacokinetic behavior of rizatriptan during co-administration with propranolol may be unpredictable. In a study of concurrent administration of propranolol 240 mg/day and a single dose of rizatriptan 10 mg in healthy subjects (n=11), mean plasma AUC and C_{max} for rizatriptan were increased by 70% and 75%, respectively, during propranolol administration. In one subject, a 4-fold increase in AUC and 5-fold increase in C_{max} was observed. This subject was not distinguishable from the others based on demographic characteristics. The AUC of the active N-monodesmethyl metabolite of rizatriptan was not affected by propranolol (see DOSAGE AND ADMINISTRATION).

Selective Serotonin Reuptake Inhibitors / Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome:
In a pharmacokinetic study with paroxetine and rizatriptan, paroxetine had no influence on the plasma levels of rizatriptan and no symptoms of serotonin syndrome emerged. Cases of life-threatening serotonin syndrome have however been reported in post-marketing experience during combined use of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans (see WARNINGS AND PRECAUTIONS.)

Drug-Food Interactions: Interactions with food have not been studied. Food has no significant effect on the bioavailability of rizatriptan but delays the time to reach peak concentration by an hour. In clinical trials, MAXALT® was administered without regard to food.

Drug-Herb Interactions: Interactions with herbal products have not been studied.

Drug-Laboratory Interactions: MAXALT® is not known to interfere with commonly employed clinical laboratory tests.

Drug-Lifestyle Interactions: Lifestyle interactions have not been established.

OVERDOSAGE

No overdoses of MAXALT® were reported during clinical trials (for more details see OVERDOSAGE in the Product Monograph).

Based on the pharmacology of rizatriptan, hypertension or other more serious cardiovascular symptoms could occur after overdosage. Gastrointestinal decontamination (i.e., gastric lavage followed by activated charcoal) should be considered in patients suspected of an overdose with MAXALT®. The elimination half-life of rizatriptan is 2 to 3 hours (see ACTION AND CLINICAL PHARMACOLOGY in the Product Monograph). Clinical and electrocardiographic monitoring should be continued for at least 12 hours, even if clinical symptoms are not observed.

There is no specific antidote to rizatriptan. In cases of severe intoxication, intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

The effects of hemo- or peritoneal dialysis on serum concentrations of rizatriptan are unknown.

(1109-a,11,07)

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ADVERTISERS INDEX

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COPAXONE®
(glatiramer acetate injection)

Treating RRMS for the long run.

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Immunomodulator

INDICATIONS AND CLINICAL USE

COPAXONE® (glatiramer acetate injection) is indicated for use in ambulatory patients with Relapsing-Remitting Multiple Sclerosis (RRMS) to reduce the frequency of relapses. The safety and efficacy of COPAXONE® in chronic progressive MS has not been established.

CONTRAINDICATIONS

COPAXONE® (glatiramer acetate injection) is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol.

Safety Information

WARNINGS

The only recommended route of administration of COPAXONE® (glatiramer acetate injection) is the subcutaneous route. COPAXONE® should not be administered by the intravenous route.

Symptoms of Potentially Cardiac Origin: Approximately 26% of COPAXONE® patients in the pre-marketing multicenter controlled trial (compared to 10% of placebo patients) experienced at least one episode of what was described as transient chest pain (see ADVERSE REACTIONS: Chest Pain). While some of these episodes occurred in the context of the Immediate post-injection reaction (see ADVERSE REACTIONS: Immediate Post-Injection Reaction), many did not. The pathogenesis of this symptom is unknown. Patients in controlled clinical trials were free of significant cardiovascular problems (New York Heart Association Class I and II) and thus the risks associated with COPAXONE® treatment for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown.

COPAXONE® has been associated with an immediate post-injection reaction consisting of a constellation of symptoms appearing immediately after injection that could include flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria (see ADVERSE REACTIONS: Immediate Post-Injection Reaction).

COPAXONE® has not been studied in patients with a history of severe anaphylactoid reactions, obstructive pulmonary disease or asthma, nor in patients under treatment for either of these two latter conditions. Particular caution is therefore advised regarding the use of COPAXONE® in such patients.

Anaphylactoid reactions associated with the use of COPAXONE® have been reported in rare instances (<1/1000) during the post-marketing period. Some cases required treatment with epinephrine and other appropriate medical treatment.

PRECAUTIONS

General: Patients should be instructed in aseptic reconstitution and self-injection techniques to assure the safe administration of COPAXONE® (glatiramer acetate injection) (see INFORMATION FOR THE PATIENT). The first injection should be performed under the supervision of an appropriately qualified healthcare professional. Patient understanding and use of aseptic self-injection techniques and procedures should be periodically re-evaluated. Patients should be cautioned against the reuse of needles or syringes and instructed in safe disposal procedures. A puncture resistant container for disposal of used needles and syringes should be used by the patient. Patients should be instructed on the safe disposal of full containers.

Considerations Involving the Use of a Product Capable of Modifying Immune Responses: **COPAXONE® is an antigenic substance and thus it is possible that detrimental host responses can occur with its use. Whether COPAXONE® can alter normal human immune responses, such as the recognition of foreign antigens is unknown. It is therefore possible that treatment with COPAXONE® may undermine the body's defenses against infections and tumor surveillance. Systematic assessments of these risks have not been done. Continued alteration of cellular immunity due to chronic treatment with glatiramer acetate might result in untoward effects.**

Glatiramer acetate reactive antibodies are formed in practically all patients exposed to daily treatment with the recommended dose. Studies in both the rat and monkey have suggested that immune complexes are deposited in the renal glomeruli. Furthermore, in a controlled clinical trial of 125 RRMS patients given glatiramer acetate 20 mg for 2 years, serum IgG levels reached at least 3 times baseline values in 80% of patients by 3 months of initiation of treatment. By 12 months of treatment, however, 30% of patients still had IgG levels at least 3 times baseline values, and 90% had levels above baseline by 12 months. The antibodies are exclusively of the IgG subtype – and predominantly of the IgG-1 subtype. No IgE type antibodies could be detected in any of the 94 sera tested.

Nevertheless, anaphylaxis can be associated with the administration of almost any foreign substance and therefore, this risk cannot be excluded.

Preclinical studies to assess the carcinogenic potential of glatiramer acetate in mice and rats do not suggest any evidence of carcinogenic potential related to glatiramer acetate administered subcutaneously at dose levels of up to 30 mg/kg/day in rats and 60 mg/kg/day in mice. The relevance of these findings for humans is unknown (see PRECAUTIONS: Considerations Involving the Use of a Product Capable of Modifying Immune Responses).

Information for Patients: To assure safe and effective use of COPAXONE®, the following information and instructions should be given to the patients:

1. COPAXONE® is not recommended for use in pregnancy. Therefore, inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while you are taking this medication.
2. Inform your physician if you are nursing.
3. Do not change the dose or dosing schedule without consulting your physician.
4. Inform your physician if you stop taking the drug.

Patients should be instructed in the use of aseptic techniques when administering COPAXONE®.

Appropriate instructions for the self-injection of COPAXONE® should be given, including a careful review of the INFORMATION FOR THE PATIENT. The first injection should be performed under the supervision of an appropriately qualified healthcare professional. Patient understanding and use of aseptic self-injection techniques and procedures should be periodically re-evaluated. Patients should be cautioned against the reuse of needles or syringes and instructed in safe disposal procedures.

Awareness of Adverse Reactions: Physicians are advised to counsel patients about adverse reactions associated with the use of COPAXONE® (see ADVERSE REACTIONS). In addition, patients should be advised to read the INFORMATION FOR THE PATIENT and resolve any questions regarding it prior to beginning COPAXONE® therapy. **Drug Interactions:** Interactions between COPAXONE® and other drugs have not been fully evaluated. Results from existing clinical trials do not suggest any significant interactions of COPAXONE® with therapies commonly used in MS patients. This includes the concurrent use of corticosteroids for up to 28 days. COPAXONE® has not been formally evaluated in combination with Interferon beta. However, 246 patients who failed on or who did not tolerate therapy with Interferon beta and were later treated with COPAXONE® within the framework of an open clinical trial, did not report any serious or unexpected adverse events thought to be related to treatment. **Laboratory Tests:** Data collected pre- and post-market do not suggest the need for routine laboratory monitoring. **Use in Pregnancy:** There are no adequate and well-controlled studies in pregnant women. No evidence of reproductive toxicity was observed in preclinical studies. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. During pre-marketing clinical trials with COPAXONE®, seven women conceived while being treated with the active drug. One case was lost to follow-up. Three of the patients electively discontinued pregnancy. Three patients stopped treatment 1, 1.5 and 2 months after learning they were pregnant; all delivered healthy babies. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, treating a nursing woman with COPAXONE® should only be considered after careful risk/benefit assessment and be used with caution. **Use in Children:** The safety and effectiveness of COPAXONE® have not been established in individuals below 18 years of age. **Use in the Elderly:** COPAXONE® has not been studied in the elderly (> 65 years old). **Use in Patients with Impaired Renal Function:** The pharmacokinetics of COPAXONE® in patients with impaired renal function have not been determined.

ADVERSE REACTIONS

In the pre-marketing clinical trials, approximately 900 individuals have received at least one dose of COPAXONE® (glatiramer acetate injection) in controlled and uncontrolled clinical trials. Total patient exposure to COPAXONE® in double-blind controlled clinical trials ranged from 6 months (693 patients) to 2 years (306 patients), with a subset of patients (n = 108) continuing up to 10 years in open-label extensions at a daily dose of 20 mg. In controlled clinical trials, the most commonly observed adverse events associated with the use of COPAXONE® which occurred at a higher frequency than in placebo-treated patients were: injection-site reactions, vasodilation, chest pain, asthenia, infection, pain, nausea, arthralgia, anxiety and hypertonia.

Of a total of 844 patients who could be evaluated for safety, approximately 8% discontinued treatment due to an adverse event. The adverse events most commonly associated with discontinuation were (in order of descending frequency): injection-site reaction (6.5%), vasodilation, unintended pregnancy, depression, dyspnea, urticaria, tachycardia, dizziness and tremor. Treatment discontinuation due to a serious adverse event considered by investigators to be related to COPAXONE® treatment included a case of life threatening serum sickness.

Immediate Post-Injection Reaction: Approximately 10% of Multiple Sclerosis patients exposed to COPAXONE® in pre-marketing studies reported a post-injection reaction immediately following subcutaneous injection of COPAXONE®. Symptoms experienced could include flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria. These symptoms were invariably transient, self-limited, did not require specific treatment and in general, arose several months after initiation of treatment, although they may

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occur earlier in the course of treatment. A given patient may experience one or several episodes of these symptoms during treatment with COPAXONE®. Whether these episodes are mediated by an immunologic or non immunologic mechanism, and whether several similar episodes seen in a given patient have identical mechanisms is unknown. In fact, whether or not this constellation of symptoms actually represents a specific syndrome is unknown. During the post-marketing period, there have been reports of patients with similar symptoms who received emergency medical care (see WARNINGS).

Chest Pain: Approximately 26% of glatiramer acetate patients in the multicenter pre-marketing controlled trial (compared to 10% of placebo patients) experienced at least one episode of what was described as transient chest pain. While some of these episodes occurred in the context of the immediate post-injection reaction described above, many did not. The temporal relationship of the chest pain to an injection of glatiramer acetate was not always known, although the pain was transient (usually lasting only a few minutes), often unassociated with other symptoms, and appeared to have no important clinical sequelae. Some patients experienced more than one such episode, and episodes usually began at least 1 month after the initiation of treatment. The pathogenesis of this symptom is unknown. There has been only one episode of chest pain during which a full ECG was performed; the ECG showed no evidence of ischemia. Patients in clinical trials were free of significant cardiovascular disease (New York Heart Association Class I or II); therefore, the risks associated with glatiramer acetate treatment for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown (see WARNINGS: Symptoms of Potentially Cardiac Origin).

ADMINISTRATION

DOSAGE AND ADMINISTRATION

COPAXONE® should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Multiple Sclerosis. The recommended dose of COPAXONE® (glatiramer acetate injection) for the treatment of Relapsing-Remitting MS is a daily injection of 20 mg given subcutaneously. For the pre-filled syringe of COPAXONE®, please see the INFORMATION FOR THE PATIENT – pre-filled syringe for instructions on the preparation and injection of COPAXONE®.

SUPPLEMENTAL PRODUCT INFORMATION

ADVERSE REACTIONS

Table 1 lists the adverse experiences after up to 35 months of treatment (> 27-33 months: COPAXONE®, n=84; Placebo, n=75; > 33 months: COPAXONE®, n=12; Placebo, n=24) in the pre-marketing multicenter placebo controlled study (Trial II) in Relapsing-Remitting Multiple Sclerosis patients that occurred at an incidence of at least 2% among patients who received COPAXONE® and at an incidence that was at least 2% more than that observed in the same trial for placebo patients regardless of their causal relationship to treatment. No laboratory adverse experiences that met these criteria were reported.

It should be noted that the figures cited in Table 1 cannot be used to predict the incidence of side effects during the course of usual medical practice, where patient characteristics and other factors differ from those that prevailed in the clinical trials. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

TABLE 1: Pre-marketing Controlled Trial in Patients with Multiple Sclerosis Adverse Experiences ≥2% Incidence and ≥2% Above Placebo

Adverse Experience		Copaxone® (n=125) N	Copaxone® (n=125) %	Placebo (n=126) N	Placebo (n=126) %
Body as a Whole	Injection-Site Pain	83	66.4	46	36.5
	Asthenia	81	64.8	78	61.9
	Injection-Site Erythema	73	58.4	17	13.5
	Injection-Site Pruritus	48	38.4	5	4.0
	Flu syndrome	38	30.4	34	27.0
	Injection-Site Inflammation	35	28.0	9	7.1
	Back pain	33	26.4	28	22.2
	Chest pain	33	26.4	13	10.3
	Injection-Site Mass	33	26.4	10	7.9
	Injection-Site Induration	25	20.0	1	0.8
	Injection-Site Welt	19	15.2	5	4.0
	Neck pain	16	12.8	9	7.1
	Face Edema	11	8.8	2	1.6
	Injection-Site Urticaria	9	7.2	0	0
	Injection-Site Hemorrhage	8	6.4	4	3.2
	Chills	5	4.0	1	0.8
	Cyst	5	4.0	1	0.8
	Injection-Site Reaction	4	3.2	1	0.8
	Injection-Site Atrophy	3	2.4	0	0
	Abscess	3	2.4	0	0
Cardiovascular	Vasodilatation	34	27.2	14	11.1
	Palpitation	14	11.2	6	4.8
	Migraine	9	7.2	5	4.0
	Syncope	8	6.4	4	3.2
Digestive	Nausea	29	23.2	22	17.5
	Vomiting	13	10.4	7	5.6
	Anorexia	6	4.8	3	2.4
	Gastroenteritis	6	4.8	2	1.6
	Oral Moniliasis	3	2.4	0	0
	Tooth Caries	3	2.4	0	0
Hemic and Lymphatic	Lymphadenopathy	23	18.4	12	9.5
	Ecchymosis	15	12.0	12	9.5
Metabolic and Nutritional	Peripheral Edema	14	11.2	7	5.6
	Weight gain	7	5.6	0	0
	Edema	5	4.0	1	0.8
Musculo Skeletal	Arthralgia	31	24.8	22	17.5
Nervous System	Hypertonia	44	35.2	37	29.4
	Tremor	14	11.2	7	5.6
	Agitation	7	5.6	4	3.2
	Confusion	5	4.0	1	0.8
	Nystagmus	5	4.0	2	1.6
Respiratory	Rhinitis	29	23.2	26	20.6
	Dyspnea	23	18.4	8	6.4
	Bronchitis	18	14.4	12	9.5
Skin and Appendages	Sweating	15	12.0	10	7.9
	Erythema	8	6.4	4	3.2
	Skin Disorder	5	4.0	2	1.6
	Skin Nodule	4	3.2	1	0.8
	Wart	3	2.4	0	0
Special Senses	Ear Pain	15	12.0	12	9.5
	Eye Disorder	8	6.4	1	0.8
Urogenital System	Urinary Urgency	20	16.0	17	13.5
	Vaginal Moniliasis	16	12.8	9	7.1
	Dysmenorrhea	12	9.6	9	7.1
	Unintended Pregnancy	4	3.2	0	0
	Impotence	3	2.4	0	0

Other events which occurred in at least 2% of patients but were present at equal or greater rates in the placebo group included:

Body as a whole: Headache, injection-site ecchymosis, accidental injury, abdominal pain, allergic rhinitis and malaise. *Digestive system:* Dyspepsia, constipation, dysphagia, fecal incontinence, flatulence, nausea and vomiting, gastritis, gingivitis, periodontal abscess, and dry mouth. *Musculoskeletal:* Myasthenia and myalgia. *Nervous system:* Dizziness, hypesthesia, paresthesia, insomnia, depression, dysesthesia, incoordination, somnolence, abnormal gait, amnesia, emotional lability, Lhermitte's sign, abnormal thinking, twitching, euphoria, and sleep disorder. *Respiratory System:* Pharyngitis, sinusitis, increased cough and laryngitis. *Skin and Appendages:* Acne, alopecia, and nail disorder. *Special Senses:* Abnormal vision, diplopia, amblyopia, eye pain, conjunctivitis, tinnitus, taste perversion, and deafness. *Urogenital System:* Urinary tract infection, urinary frequency, urinary incontinence, urinary retention, dysuria, cystitis, metrorrhagia, breast pain, and vaginitis.

Data on adverse events occurring in the controlled clinical trials were analyzed to evaluate gender related differences. No clinically significant differences were identified. In these clinical trials 92% of patients were Caucasian, which is representative of the population of patients with Multiple Sclerosis. In addition, the vast majority of patients treated with COPAXONE® were between the ages of 18 and 45. Consequently, inadequate data are available to perform an analysis of the incidence of adverse events related to clinically relevant age subgroups.

Laboratory analyses were performed on all patients participating in the clinical program for COPAXONE®. Clinically significant changes in laboratory values for hematology, chemistry, and urinalysis were similar for both COPAXONE® and placebo groups in blinded clinical trials. No patient receiving COPAXONE® withdrew from any trial due to abnormal laboratory findings.

Other Adverse Events Observed During All Clinical Trials: COPAXONE® has been administered to approximately 900 individuals during clinical trials, only some of which were placebo controlled. During these trials, all adverse events were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using COSTART II dictionary terminology. All reported events that occurred at least twice and potentially important events occurring once, are included except those already listed in the previous table, those too general to be informative, trivial events, and other events which occurred in at least 2% of treated patients and were present at equal or greater rates in the placebo group. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: Frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients. *Body as a whole: Frequent:* injection-site edema, injection-site atrophy, abscess and injection-site hypersensitivity. *Infrequent:* injection-site hematoma, injection-site fibrosis, moon face, cellulitis, generalized edema, hernia, injection-site abscess, serum sickness, suicide attempt, injection-site hypertrophy, injection-site melanosis, lipoma and photosensitivity reaction. *Cardiovascular: Frequent:* Hypertension. *Infrequent:* Hypotension, midsystolic click, systolic murmur, atrial fibrillation, bradycardia, fourth heart sound, postural hypotension and varicose veins, hypotension and varicose veins. *Digestive: Infrequent:* Dry mouth, stomatitis, burning sensation on tongue, cholecystitis, colitis, esophageal ulcer, esophagitis, gastrointestinal carcinoma, gum hemorrhage, hepatomegaly, increased appetite, melena, mouth ulceration, pancreas disorder, pancreatitis, rectal hemorrhage, tenesmus, tongue discoloration and duodenal ulcer. *Endocrine: Infrequent:* Goiter, hyperthyroidism, and hypothyroidism. *Gastrointestinal: Frequent:* Bowel urgency, oral moniliasis, salivary gland enlargement, tooth caries, and ulcerative stomatitis. *Hemic and Lymphatic: Infrequent:* Leukopenia, anemia, cyanosis, eosinophilia, hematemesis, lymphedema, pancytopenia, and splenomegaly. *Metabolic and Nutritional: Infrequent:* Weight loss, alcohol intolerance, Cushing's syndrome, gout, abnormal healing, and xanthoma. *Musculoskeletal: Infrequent:* Arthritis, muscle atrophy, bone pain, bursitis, kidney pain, muscle disorder, myopathy, osteomyelitis, tendon pain, and tenosynovitis. *Nervous: Frequent:* Abnormal dreams, emotional lability, and stupor. *Infrequent:* Aphasia, ataxia, convulsion, circumoral paresthesia, depersonalization, hallucinations, hostility, hypokinesia, coma, concentration disorder, facial paralysis, decreased libido, manic reaction, memory impairment, myodonus, neuralgia, paranoid reaction, paraplegia, psychotic depression and transient stupor. *Respiratory: Frequent:* Hyperventilation, hay-fever. *Infrequent:* Asthma, pneumonia, epistaxis, hypoventilation, and voice alteration. *Skin and Appendages: Frequent:* Eczema, herpes zoster, pustular rash, skin atrophy and warts. *Infrequent:* Dry skin, skin hypertrophy, dermatitis, furunculosis, psoriasis, angioedema, contact dermatitis, erythema nodosum, fungal dermatitis, maculopapular rash, pigmentation, benign skin neoplasm, skin carcinoma, skin striae, and vesiculobullous rash. *Special Senses: Frequent:* Visual field defect. Infrequent: Dry eyes, otitis externa, ptosis, cataract, corneal ulcer, mydriasis, optic neuritis, photophobia, and taste loss. *Urogenital: Frequent:* Amenorrhea, hematuria, impotence, menorrhagia, suspicious Papanicolaou smear, urinary frequency and vaginal hemorrhage. *Infrequent:* Vaginitis, flank pain (kidney), abortion, breast engorgement, breast enlargement, breast pain, carcinoma cervix *in situ*, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

Adverse events reported post-marketing and not previously noted in clinical trials: Post-marketing experience has shown an adverse event profile similar to that presented above. Reports of adverse reactions occurring under treatment with COPAXONE® (glatiramer acetate) not mentioned above, that have been received since market introduction and that may have or not have causal relationship to the drug include the following: *Body as a Whole:* Sepsis, LE syndrome, hydrocephalus, enlarged abdomen, injection-site hypersensitivity, allergic reaction, anaphylactoid reaction, bacterial infection, fever, infection. *Cardiovascular:* Thrombosis, peripheral vascular disease, pericardial effusion, myocardial infarct, deep thrombophlebitis, congestive heart failure, cardiomyopathy cardiomegaly, arrhythmia, angina pectoris, tachycardia. *Digestive:* Tongue edema, stomach ulcer hemorrhage, liver function abnormality, liver damage, hepatitis, eructation, cirrhosis of the liver, cholelithiasis, diarrhea, gastrointestinal disorder. *Hemic and Lymphatic:* Thrombocytopenia, lymphoma-like reaction, acute leukemia. *Metabolic and Nutritional:* Hypercholesteremia. *Musculoskeletal:* Rheumatoid arthritis, generalized spasm. *Nervous:* Myelitis, meningitis, CNS neoplasm, cerebrovascular accident, brain edema, abnormal dreams, aphasia, convulsion, neuralgia, anxiety, foot drop, nervousness, speech disorder, vertigo. *Respiratory:* Pulmonary embolus, pleural effusion, carcinoma of lung, hay fever, laryngismus. *Skin and Appendages:* Herpes simplex, pruritis, rash, urticaria. *Special Senses:* Glaucoma, blindness, visual field defect. *Urogenital:* Urogenital neoplasm, urine abnormality, ovarian carcinoma, nephrosis, kidney failure, breast carcinoma, bladder carcinoma, urinary frequency. **Localized Adverse Reactions Associated with subcutaneous use:** At injection sites, localized lipoatrophy and, rarely, injection-site skin necrosis have been reported during post-marketing experience. Lipoatrophy may occur after treatment onset (sometimes as early as several months) and may be permanent. There is no known therapy for lipoatrophy. To assist in possibly minimizing these events the patient should be advised to follow proper injection technique and to rotate injection areas and sites on a daily basis. (see INFORMATION FOR THE PATIENT)

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdose with COPAXONE® has been reported in three patients. One patient injected four doses (80 mg total) of COPAXONE® at once. No sequelae were noted. Two other patients, a 28-year old male and a 37-year old female, were given 3 injections of 20 mg of COPAXONE® at one half hour intervals by error. Neither patient evidenced any change in blood pressure, heart rate, or temperature. Telephone follow up several hours later produced no report of adverse experiences from either patient. The maximum COPAXONE® dose reported in an overdose case is 80 mg glatiramer acetate injection.

Based on Product Monograph dated April 2, 2008. Product Monograph available on request.

See our AD on pages A-5

PrLYRICA® PREGABALIN

PRESCRIBING SUMMARY

PATIENT SELECTION CRITERIA

THERAPEUTIC CLASSIFICATION: Analgesic Agent

INDICATIONS AND CLINICAL USE

LYRICA is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia in adult patients.

LYRICA may be useful in the management of central neuropathic pain in adult patients for which it has been issued marketing authorization with conditions to reflect the promising nature of the clinical evidence and the need for a confirmatory study to verify its clinical benefit. Patients should be advised of the nature of the authorization.

CONTRAINDICATIONS: Patients who are hypersensitive to pregabalin or to any ingredient in the formulation or component of the container.

SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Tumorigenic Potential: In standard preclinical in vivo lifetime carcinogenicity studies of pregabalin, a high incidence of hemangiosarcoma was identified in two different strains of mice. The clinical significance of this finding is uncertain. Clinical experience during pregabalin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

Ophthalmological Effects: In controlled studies, pregabalin treatment was associated with vision-related adverse events such as blurred vision (amblyopia) (6% pregabalin and 2% placebo) and diplopia (2% pregabalin and 0.5% placebo). Approximately 1% of pregabalin-treated patients discontinued treatment due to vision-related adverse events (primarily blurred vision). Of the patients who did not withdraw, the blurred vision resolved with continued dosing in approximately half of the cases (see Product Monograph, **Post-Marketing Adverse Drug Reactions**).

Patients should be informed that if changes in vision occur, they should notify their physician.

Peripheral Edema: In controlled clinical trials pregabalin treatment caused peripheral edema in 6% of patients (336/5508) compared with 2% of patients (42/2,384) in the placebo group. In these studies, 0.5% (28/5508) of pregabalin patients and 0.2% (4/2,384) of placebo patients withdrew due to peripheral edema (see Product Monograph, **ADVERSE REACTIONS, Peripheral Edema**).

In controlled clinical trials of up to 13 weeks in duration of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. In the same trials, peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

Higher frequencies of weight gain and peripheral edema were observed in patients taking both LYRICA (pregabalin) and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone.

As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, care should be taken when co administering LYRICA and these agents.

Congestive Heart Failure: In controlled clinical studies, events of congestive heart failure were reported at an infrequent rate (between 0.1% and 1%; see Product Monograph, **ADVERSE REACTIONS, Less Common Clinical Trial Adverse Reactions**).

There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin (see Product Monograph, **ADVERSE REACTIONS, Post-marketing Adverse Drug Reactions**). These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic pain indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

Weight Gain: Pregabalin treatment was associated with weight gain. In pregabalin controlled clinical trials of up to 13 weeks, a gain of 7% or more over baseline weight was observed in 8% of pregabalin treated patients and 2% of placebo-treated patients. Few patients treated with pregabalin (0.2%) withdrew from controlled trials due to weight gain (see Product Monograph, **ADVERSE REACTIONS**, **Weight Gain**). Pregabalin-associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline BMI, gender, or age. Weight gain was not limited to patients with edema (see Product Monograph, **WARNINGS AND PRECAUTIONS, Peripheral Edema**).

Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of pregabalin-associated weight gain are unknown.

While the effects of pregabalin-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open label clinical trials with diabetic patients, pregabalin treatment did not appear to be associated with loss of glycemic control (as measured by HbA_{1C}).

Dizziness and Somnolence: In controlled neuropathic pain studies, pregabalin caused dizziness in 23% of patients (424/1,831) compared to 7% in placebo (58/857). Somnolence was experienced by 14% (256/1,831) and 4% (33/857) of the patients treated with pregabalin and placebo, respectively. These events begin shortly after the initiation of therapy and generally occur more frequently at higher doses.

Abrupt or Rapid Discontinuation: Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, and diarrhea. Pregabalin should be tapered gradually over a minimum of one week rather than discontinued abruptly (see Product Monograph, **ADVERSE REACTIONS**, **Adverse Events Following Abrupt or Rapid Discontinuation**).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions: *Most Common Adverse Events in All Pre-marketing Controlled Clinical Studies of Peripheral Neuropathic Pain*: The most commonly observed adverse events (≥5% and twice the rate of that seen in placebo) in pregabalin-treated patients were: dizziness, somnolence, peripheral edema, and dry mouth. Adverse events were usually mild to moderate in intensity.

Adverse Events From a Controlled Clinical Study in Central Neuropathic Pain Associated With Spinal Cord Injury: The most commonly observed treatment-related adverse events (≥5% and twice the rate of that seen in placebo) in pregabalin-treated patients were: somnolence, dizziness, asthenia, dry mouth, edema, myasthenia, constipation, thinking abnormal, amblyopia, and amnesia. Adverse events were usually mild to moderate in intensity.

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by telephone: 1-866-234-2345.

ADMINISTRATION

Dosing Considerations

Patients with Impaired Renal Function: **Pregabalin is primarily eliminated from the systemic circulation by renal excretion as unchanged drug. In patients with a medical history of significant renal insufficiency, daily dosages should be reduced accordingly (see Table in Supplemental Product Information).**

Adults:

Neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia: The recommended starting dose for LYRICA is 150 mg/day, given in two or three divided doses (75 mg BID or 50 mg TID), with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Efficacy of LYRICA has been demonstrated within the first week. Based on individual patient response and tolerability, the dose may be increased to 150 mg BID (300 mg/day) after one week.

For patients who experience significant and ongoing pain and can tolerate pregabalin 300 mg/day well, maximum daily dose of 600 mg (300 mg BID) can be used. However, in clinical trials, LYRICA 600 mg/day did not provide additional significant efficacy and patients treated with this dose experienced markedly higher rates of adverse events and discontinued the trial more frequently.

Central neuropathic pain: The recommended starting dose for LYRICA is 150 mg/day, given in two divided doses (75 mg BID), with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Efficacy of LYRICA has been demonstrated within the first week. Based on individual patient response and

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tolerability, the dose may be increased to 150 mg BID (300 mg/day) after one week.

For patients who experience significant and ongoing pain and can tolerate pregabalin 300 mg/day well, a maximum daily dose of 600 mg (300 mg twice a day, BID) may be considered.

Administration: LYRICA is given orally with or without food.

Supplemental Product Information

Special Populations: ***Geriatrics (≥65 years of age):*** Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in creatinine clearance. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function (see Product Monograph, **WARNINGS AND PRECAUTIONS**, **Geriatrics >65 years of age**).

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. Pregabalin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labour and Delivery: The effects of pregabalin on labour and delivery in pregnant women are unknown.

Nursing Women: It is not known if pregabalin is excreted in human breast milk; however, it is present in the milk of rats. Because of the potential for adverse reactions in nursing infants from pregabalin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics (<18 years of age): The safety and efficacy of pregabalin in pediatric patients (<18 years of age) have not been established and its use in this patient population is not recommended (see Product Monograph, **WARNINGS AND PRECAUTIONS**, **Pediatrics**).

WARNINGS AND PRECAUTIONS: See the Product Monograph for further information on the following: tumorigenic potential, ophthalmological effects, peripheral edema, congestive heart failure, weight gain, dizziness and somnolence, sexual function/reproduction, and special populations.

DRUG INTERACTIONS

Overview: Since pregabalin is predominately excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), does not inhibit drug metabolism in vitro, and is not bound to plasma proteins, LYRICA (pregabalin) is unlikely to produce, or be subject to, pharmacokinetic interactions.

Drug Abuse and Dependence/Liability: Pregabalin is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behaviour).

ADMINISTRATION

Dosage Adjustment Based on Renal Function: Dosing adjustment should be based on creatinine clearance (Cl_{cr}), as indicated in Table 1.

Pregabalin is effectively removed from plasma by hemodialysis. Over a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients receiving hemodialysis, pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose adjustment, a supplemental dose should be given immediately following every 4-hour hemodialysis treatment (see Table below).

Table 1. Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (Cl_{cr}) (mL/min)	Total Pregabalin Daily Dose (mg/day)[a] Recommended Dose Escalation*			Dose Regimen
	Starting dose		Maximum daily dose	
≥60	150	300	600	BID or TID
30-60	75	150	300	BID or TID
15-30	25-50	75	150	QD or BID
<15	25	25-50	75	QD
Supplementary dosage following hemodialysis (mg)[b]				
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg Patients on the 25-50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg				

TID = Three divided doses; BID = Two divided doses; QD = Single daily dose.
* Based on individual patient response and tolerability.
a Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.
b Supplementary dose is a single additional dose.

OVERDOSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans: The highest known dose of pregabalin received in the clinical development program was 15,000 mg in 1 patient. The types of adverse events experienced by patients who received an overdose were not clinically different from other patients receiving recommended doses of pregabalin.

Treatment or Management of Overdose: There is no specific antidote for overdose with pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with pregabalin.

Hemodialysis: Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours) and should be considered in cases of overdose. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

AVAILABILITY OF DOSAGE FORMS

LYRICA is available in dosage strengths of 25 mg, 50 mg, 75 mg, 100 mg,* 150 mg, 200 mg,* 225 mg,* and 300 mg capsules.

* Not commercially available in Canada

For a copy of the Product Monograph or full Prescribing Information, please contact: Pfizer Canada Medical Information at 1-800-463-6001 or visit www.pfizer.ca.

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The Canadian Neurological Sciences Federation is pleased to recognize our Sponsors* for 2008. These organizations partner with CNSF to determine the causes of, and develop treatment for diseases and injuries of the nervous system, and in the care of patients with these diseases and injuries. Along with support of the Canadian Journal of Neurological Sciences and other initiatives the CNSF maintains throughout the year, these organizations graciously provided unrestricted educational grants to the Annual Congress, this year in Victoria, British Columbia; June 17th – 20, 2008.

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CANADIAN NEUROLOGICAL SCIENCES FEDERATION
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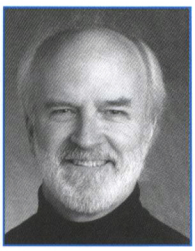

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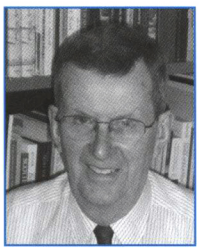

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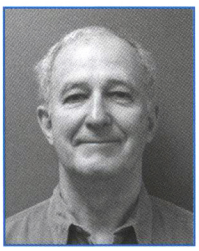

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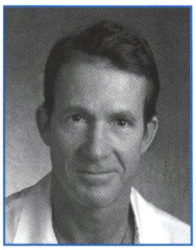

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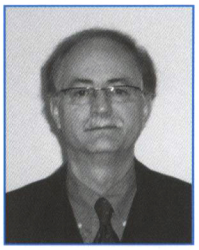

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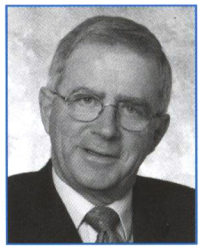

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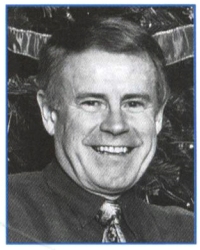

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CNSF - *Canadian Neurological Sciences Federation;* NSFC - *Neurological Sciences Foundation of Canada;* CNS - *Canadian Neurological Society;* CNSS - *Canadian Neurosurgical Society;* CSCN - *Canadian Society of Clinical Neurophysiologists;* CACN - *Canadian Association of Child Neurology;* CBANHC - *Canadian Brain and Nerve Health Coalition*

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PrAGGRENOX® PROVIDES STRONG DEFENSE AGAINST A SECOND STROKE

- **AGGRENOX® prevented *twice* as many strokes vs. ASA alone[1,2,3*]**
  - 22.1% additional stroke protection over ASA (p=0.008)[2†]
  - 36.8% greater stroke protection vs. placebo (p<0.001)[2†]
- **Proven safety profile[2]**
- **ASA/extended release dipyridamole is recommended as first-line secondary stroke prevention therapy in:**
  - Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy[4]
  - European Stroke Initiative (EUSI)[5]
  - UK Royal College Physician Guidelines[6]

* Randomized, double-blind, placebo-controlled trial, 6,602 patients with history of TIA or ischemic stroke. AGGRENOX® 50 mg ASA + 400 mg extended release dipyridamole per day (b.i.d. dosing) n=1,650, ASA 50 mg per day (25 mg b.i.d.) n=1,649, placebo n=1,649, extended release dipyridamole 400 mg per day (200 mg b.i.d.) n=1,654. For every 1,000 patients treated for two years, AGGRENOX® prevented 58 strokes vs. only 29 for ASA, compared to placebo.[1,2,3]

† Percentage of patients experiencing a stroke within two years: AGGRENOX® 9.5%, ASA 12.5%, placebo 15.2%.[2]

AGGRENOX® is indicated for the prevention of stroke in patients who have had a previous stroke or a transient ischemic attack (TIA).

The overall discontinuation rate due to adverse events was 27.8% for AGGRENOX®, 23.2% for ASA, and 23.7% for placebo.

AGGRENOX® is contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drug products; patients with the syndrome of asthma, rhinitis and nasal polyps; and in patients with hypersensitivity to dipyridamole, ASA, or any of the other product components.

AGGRENOX® contains approximately 23 mg sucrose and 106 mg of lactose per maximum recommended daily dose. Patients with rare hereditary problems of fructose intolerance and/or galactose intolerance (e.g. galactosaemia) should not take this medicine.

If a patient is to undergo elective surgery, consideration should be given to discontinue AGGRENOX® 10 days prior to surgery, to allow for the reversal of effect.

The use of AGGRENOX® may increase the risk of bleeding such as skin haemorrhage, gastrointestinal bleeding and intracerebral haemorrhage. The addition of other antiplatelet agents (e.g. Clopidogrel, Ticlopidine) to AGGRENOX® may further increase the risk of serious bleeding and is not recommended.

Due to the ASA component of AGGRENOX® should be: avoided in patients with severe hepatic insufficiency or severe renal failure, avoided in patients with a history of active peptic ulcer disease, and used with caution in patients with inherited or acquired bleeding disorders, nursing mothers, patients taking selective serotonin reuptake inhibitors (SSRIs) or corticosteroids, or in patients who consume three or more alcoholic drinks per day.

AGGRENOX® should not be used in paediatric patients or during the third trimester of pregnancy.

AGGRENOX® has a vasodilatory effect and should be used with caution in patients with severe coronary artery disease (e.g. unstable angina or recently sustained myocardial infarction).

The most common adverse events with AGGRENOX® was headache (39.2% vs. 33.8% for ASA and 32.9% for placebo), dyspepsia (18.4% vs. 18.1% for ASA, and 16.7% for placebo), abdominal pain (17.5% vs. 15.9% for ASA and 14.5% for placebo), nausea (16.0% vs. 12.7% for ASA and 14.1% for placebo), and diarrhea (12.7% vs. 6.8% for ASA and 9.8% for placebo). When headache occurred it was particularly evident in the first month of therapy. 8.9% of patients discontinued due to headache, 66% of these discontinued within the first month.

Discontinuation rates due to headache were 2.8% and 2.1% in the placebo and ASA group respectively.

Consult Prescribing Information for complete details.

References: **1.** Diener HC, *et al.* European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *Journal of the Neurological Sciences* 1996;143:1-13. **2.** AGGRENOX® Product Monograph. Boehringer Ingelheim (Canada) Ltd. July 2006. **3.** Diener HC, *et al.* European Stroke Prevention Study 2. Efficacy and Safety Data. *Journal of the Neurological Sciences* 1997;151:S1-S77. **4.** Albers GW, Amarenco P, Easton DJ, Sacco RL, Teal P. Antithrombotic and Thrombolytic Therapy for Ischemic Stroke. Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *CHEST* 2004;126:483S-512S.

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PrAggrenox®
ASA /Extended Release Dipyridamole

Challenging the benchmark in secondary stroke prevention[1,4,5,6]

For brief prescribing information see pages A-16 to A-18

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